

Drug Selection in a Patient With a History of Hypersensitivity Reactions: A Practical Approach for the Orthopedist

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Drug allergies are specific to characteristics of the medication's chemical structure.

Patients with a history of ≥ 1 or more medication allergies are common in the surgical population. In one study, 29.1% of patients attending a pre-admission surgical clinic reported having at least one drug allergy.¹ Most of the reported allergies were to antibiotics, opioid analgesics, or nonsteroidal anti-inflammatory drugs (NSAIDs), drug classes frequently prescribed by orthopedists. Noting these reactions is important, as is determining whether the reported allergy is a true allergy or a non-allergic

adverse drug event. Management of a patient with a history of hypersensitivity reactions can be complex. This article reviews allergies and alternative medication strategies relevant to the drugs commonly prescribed by the orthopedic practitioner, with a specific focus on cross-reactivity within the classes of beta-lactam antibiotics, opioids, NSAIDs, and local anesthetics. This article will also discuss medication selection in patients with allergies to sulfonamide antibiotics, clindamycin, tramadol, medications commonly prescribed for the treatment of osteoporosis, and products containing glucosamine and chondroitin.

IMMUNOLOGY OF AN ALLERGIC REACTION

A true medication allergy is immune-mediated via complement, sensitized T-lymphocytes or a humoral response. The time

to onset of an allergic reaction is variable and dependent on the mechanism of immune response as well as prior exposure to the medication. Table 1 describes drug hypersensitivities as classified by their mechanism, time of onset, and clinical signs and symptoms.² Additionally, medication allergies are specific to characteristics of the chemical structure. These processes can be contrasted with non-allergic drug intolerances, such as Red-Man Syndrome with vancomycin and pruritus caused by codeine, both of which are due to histamine release from mast cells. With vancomycin, the reaction is related to the infusion rate.³ Other reactions, such as heparin-induced thrombocytopenia, may have an immune component, yet are not reflective of a hypersensitivity and therefore are not classified as an allergy.⁴

ANTIMICROBIALS

Antibiotics are frequently used by orthopedists for surgical prophylaxis, empiric therapy, and treatment of in-

fections. Patients commonly report allergies to these agents, thus it is important to distinguish between true medication allergies and those that are adverse drug events.¹ An additional consideration with antibiotics, specifically beta-lactam antibiotics, is the likelihood of cross-reactivity between classes to prevent exclusion of useful medications.

Beta-lactam Antibiotics

Beta-lactams are a commonly prescribed group of antibiotics, including penicillins, cephalosporins, carbapenems and monobactams. Up to 90% of reported allergies to penicillins are not true allergies, and the patient may receive a penicillin safely.⁵ A true beta-lactam allergy typically consists of a skin rash, urticaria, or edema, with anaphylaxis occurring rarely.¹ Stevens-Johnson syndrome, a diffuse erythematous reaction with mucous membrane involvement and skin sloughing, also can occur with beta-lactams.^{2,6}

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Table 1

Gell and Coombs Classification of Drug Hypersensitivity Reactions *

Classification	Antibody	Timing	Clinical Presentation
Type I	IgE	Minutes to 2 hours; usually occurs after the second exposure to the drug; may be delayed for up to 48 hours postexposure	Anaphylaxis, isolated urticaria, angioedema, bronchospasm, abdominal cramping, respiratory arrest, cardiovascular collapse, arrhythmias
Type II	IgG or IgM	7-21 days after initiation of the drug	Cytopenias (hemolytic anemia, thrombocytopenia, some neutropenias), vasculities (some)
Type III	IgG or IgM	5-21 days after initiation of the drug	Serum-sickness like illness, vasculities (some), morbilliform or maculopapular rash, urticaria (late onset), glomerulonephritis, interstitial nephritis, erythema multiforme, Stevens-Johnson syndrome
Type IV	Sensitized T Lymphocyte	Variable; usually within 24-48 hours post-drug exposure	Contact dermatitis, exanthematous reactions (including maculopapular rash), bullous or pustular eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial pneumonitis, granulomatous hepatitis

*Adapted with permission from the American Society of Health-System Pharmacists.²

Cross-sensitivities between the beta-lactams are variable. Patients with a history of a life-threatening allergy to any of the beta-lactams should not be given a penicillin, cephalosporin or carbapenem. Skin testing may be performed in patients reporting allergies to penicillins, especially if their desired treatment includes a beta-lactam antibiotic.⁷ If the patient has a negative skin test, other beta-lactam antibiotics may be considered for administration; a negative skin test does not necessarily rule out cross-sensitivity to these agents. In patients who report less severe reactions, more options exist. Cross-sensitivity occurs more frequently between penicillins and first-generation cephalosporins than between penicillins and second- or third-generation cephalosporins. In many cases, a newer cephalosporin will be tolerated in a patient with a history of an allergy to a penicillin or a first-generation cephalosporin.^{6,8} Likewise, a patient allergic to a first-generation cephalosporin is more likely to have

cross-sensitivity to a penicillin than a patient allergic to a newer cephalosporin.⁶

Carbapenems should be avoided in patients with a penicillin allergy, as imipenem has been found to have up to 50% cross-reactivity with penicillin allergies.⁷ While meropenem has no reports of cross-reactivity, it is not recommended for use in patients with a severe penicillin allergy. The cross-reactivity of carbapenems with cephalosporin allergies is unknown, but speculated to be low (due to most cephalosporin allergies being related to side chains not present in the chemical structure of carbapenems). The monobactam aztreonam is generally safe for use in patients with a beta-lactam allergy, with the exception of ceftazidime (due to structurally similar side chains).⁶

Allergies to Sulfonamide Antibiotics

Another frequently reported allergy is to sulfonamide antibiotics. A true allergic reaction to

a sulfonamide is characterized by fever, maculopapular rash, and organ toxicity (eg, hepatitis) developing after 1 to 2 weeks of treatment.³ Stevens-Johnson syndrome also may occur. This class is frequently implicated in allergic reactions, especially among older patients. In most instances, use of a different class of antibiotics is appropriate, as there are no reports of cross-reactivity. Patients with an allergy to a sulfonamide antibiotic should use caution when taking other medications with a sulfa moiety (eg, furosemide or celecoxib). This may not preclude their use as not all sulfa drugs have the structural characteristics of the sulfonamides that are implicated in allergic reactions. Patients should be advised of possible risks, and appropriately monitored when initiating therapy with another sulfa drug.

Allergies to Clindamycin and its Cross-reactivity

Clindamycin is frequently used for surgical prophylaxis, especially in patients with al-

lergies to other classes of antibiotics. True clindamycin allergies typically manifest as a rash (frequently reported as being erythematous, pruritic or maculopapular), exanthema or skin exfoliation occurring during the first 1 to 2 weeks of treatment.⁹ Anaphylactic reactions to clindamycin are rare.¹⁰ Clindamycin, a derivative of lincomycin, has no reports of cross-reactivity with other antibiotic classes, including the macrolide antibiotics. Alternative therapy should consist of another agent and be tailored to infection-specific characteristics.

HYPERSENSITIVITY REACTIONS TO ANALGESICS AND LOCAL ANESTHETICS

Post-surgical and chronic pain are issues frequently addressed by orthopedic practitioners. Medication therapy for pain frequently consists of opioids, tramadol, or NSAIDs, while local anesthetics are used for management of procedure-related pain. As many patients report allergies to ≥ 1

Table 2

Medication Selection* Based on Reported Allergy

Allergen	Representative Drugs in Class	Alternative Medication
Beta-lactam antibiotics		
Penicillins (anaphylaxis)	Penicillin, amoxicillin, amoxicillin/clavulanic acid, ampicillin, ampicillin/sulbactam, nafcillin, dicloxacillin, ticarcillin/clavulanate, piperacillin, piperacillin/tazobactam	Non beta-lactam, aztreonam
Penicillins (non-anaphylactic)	See above	Cephalosporin, carbapenem, monobactam, non beta-lactam
Cephalosporins (anaphylaxis)	See below	Non beta-lactam, aztreonam
1st generation cephalosporins (non-anaphylactic)	Cefazolin, cephalexin, cefadroxil	2nd or 3rd generation cephalosporin, monobactam, non beta-lactam
2nd and 3rd generation cephalosporins (non-anaphylactic)	2nd generation: cefuroxime, cefoxitin, cefprozil, cefaclor; 3rd generation: cefpodoxime, cefdinir, cefibuten, cefixime, ceftriaxone, ceftizoxime, cefotaxime, ceftazidime	Penicillin, 1st generation cephalosporin, monobactam, meropenem, non beta-lactam
Monobactams	Aztreonam	Another beta-lactam (excluding ceftazidime), non beta-lactam
Carbapenems	Imipenem, meropenem, ertapenem	2nd or 3rd generation cephalosporin, monobactam, non beta-lactam
Opioids		
Morphine-like	Morphine, codeine, hydrocodone, oxycodone, hydromorphone, oxymorphone	Meperidine- or methadone-like opioid
Meperidine-like	Meperidine, fentanyl	Morphine- or methadone-like opioid
Methadone-like	Methadone, propoxyphene	Morphine- or meperidine-like opioid
Tramadol	Tramadol	Meperidine- or methadone-like opioid
NSAIDs		
Propionic acids	Ibuprofen, fenoprofen, ketoprofen, naproxen	APAP, celecoxib, oxycam or acetic acid NSAIDs, tramadol
Acetic acids	Diclofenac, etodolac, ketorolac, sulindac, nabumetone	APAP, celecoxib, oxycam or propionic acid NSAIDs, tramadol
Oxicams	Meloxicam, piroxicam	APAP, celecoxib, propionic acid or acetic acid NSAIDs, tramadol
Local Anesthetics		
Esters	Benzocaine, chloroprocaine, procaine	Amide local anesthetic
Amides	Bupivacaine, lidocaine, mepivacaine, prilocaine	Ester local anesthetic

Abbreviations: APAP=acetaminophen and NSAIDs=nonsteroidal anti-inflammatory drugs.

*Medications may not be available in both intravenous and oral dosage forms.

of these medications, knowledge of cross-reactivity is an integral component of effective pain management.

Opioid Hypersensitivity and Cross-reactivity

The opioids can be separated into natural, semi-synthetic, and synthetic classes, or by their

chemical structure (morphine-like, meperidine-like, or methadone-like).¹¹ Allergies to opioids are generally limited to a structural subclass. Allergic reactions due to opioids typically include urticaria or other skin rashes, and rarely anaphylaxis. Wheals or itching at the injection site, flushing, or hypotension are re-

lated to histamine release and are not allergies. A patient with a true allergy to an opioid should receive a structurally dissimilar opioid (Table 2). Patients with a true allergy to morphine also should avoid codeine, which is metabolized to morphine.¹²

Tramadol is a centrally acting analgesic used as an alternative

to NSAIDs or more potent opioids for the treatment of moderate pain. True tramadol allergies are rare (occurring in <0.1% in one study),¹³ and typically involve hives or pruritus, but can include anaphylaxis or Stevens-Johnson syndrome. Tramadol is structurally similar to morphine and codeine, so cross-reactivity

can be expected. The package insert cautions against use of tramadol in any reported opioid allergy.^{13,14}

NSAID Hypersensitivity and Cross-reactivity

Nonsteroidal anti-inflammatory drugs are used for the treatment of pain and in some inflammatory disease states. True allergies to NSAIDs are characterized by urticaria and angioedema; anaphylaxis occurs rarely.¹⁵ Nonsteroidal anti-inflammatory drugs can be differentiated by their chemical structures into classes,¹⁶ (Table 2). Acetaminophen, tramadol, or a cyclooxygenase 2 (COX-2) inhibitor are useful alternatives in patients with a true NSAID allergy.¹⁷ If an NSAID must be used, consider an agent from another class (Table 2).

Many pseudoallergic reactions to NSAIDs exist, such as NSAID- or aspirin-induced rhinitis, asthma, or skin reactions, that have been described in full elsewhere.^{17,18} Nonsteroidal anti-inflammatory drugs should be avoided in patients reporting any of the following conditions caused or worsened by NSAIDs or aspirin: bronchoconstriction, asthma, nasal polyps, or acute worsening of chronic urticaria. If any of these events occur in a patient given NSAIDs, the patient should be evaluated by a physician experienced with these reactions. Acetaminophen at low to medium doses generally is safe in these patients; however, some cross-sensitivity has been reported when using COX-2 inhibitors.¹⁷

Local Anesthetic Hypersensitivity and Cross-reactivity

True allergies to local anesthetics are rare (<1% of reported reactions), and can be immediate or delayed.¹⁹ The immediate reactions generally involve¹⁷ local or systemic urticaria with anaphylactic symptoms, while the delayed reactions typically present as contact dermatitis. Local anesthetics are classified as esters or amides based on the linking bond of their chemical structure. True allergies occur more frequently with the esters, which are metabolized to para-aminobenzoic acid (PABA). Patients reporting an allergy to an ester anesthetic should be given an amide anesthetic, and patients reporting an allergy to an amide should be given an ester, as these classes do not typically cross-react (Table 2). However, it is important to consider that the preservatives in many local anesthetics are structurally similar to PABA, and could elicit an allergic reaction in a sensitive patient even when using an amide.

HYPERSENSITIVITY REACTIONS TO OSTEOPOROSIS MEDICATIONS

Multiple products with different mechanisms of action are available for the treatment of osteoporosis, including calcitonin, bisphosphonates, raloxifene, and teriparatide. As a general rule, if a patient reports an allergy to one of these medications it is advisable to use a medication from another class.

Calcitonin Hypersensitivity

Calcitonin is available in intramuscular and intranasal dosage forms. Injection site reactions with the intramuscular product and nasal irritation with the intranasal product are not immunologic in nature. Yet, there have been reports of hypersensitivity reactions, consisting of urticaria and anaphylaxis, with the intramuscular formulation.²⁰ Although case reports exist of patients previously able to tolerate the intranasal product who later developed hypersensitivity reactions to the intramuscular product, using intranasal calcitonin in a patient with a history of hypersensitivity to the intramuscular dosage form is not recommended.^{21,22} In patients with a true calcitonin allergy, a medication from another class would be suggested.

Bisphosphonate Hypersensitivity

A number of bisphosphonate products currently are available, including alendronate, ibandronate and risedronate. The literature contains case reports of an allergic rash occurring with bisphosphonates, primarily alendronate.²³ Currently, no information exists regarding cross-reactivity with other bisphosphonates, but treatment with a structurally dissimilar medication is recommended.²⁴

Raloxifene Hypersensitivity

Raloxifene is a selective estrogen receptor modulator used in the treatment of osteoporosis in postmenopausal women.²⁴ Hypersensitivity reactions to raloxifene have not yet been

characterized in the literature. A medication from a different class should be used in patients reporting a raloxifene allergy.

Teriparatide Hypersensitivity

Teriparatide (recombinant human parathyroid hormone) is administered subcutaneously daily to stimulate new bone formation. Due to the agent's unique mechanism of action and the risk of developing osteosarcoma, the US Food and Drug Administration recommends a maximum duration of use of 2 years, and only in patients for whom the benefits outweigh the potential risks of treatment.²⁵ Hypersensitivity reactions to teriparatide have not yet been characterized in the literature. In patients reporting an allergy, a medication from a different class should be used.

GLUCOSAMINE AND CHONDROITIN HYPERSENSITIVITY CONCERNS

Products containing glucosamine and chondroitin are used by many patients in the treatment of osteoarthritis. One concern when initiating a patient on these products is that glucosamine usually is obtained from the shells of shrimp or other crustacea. Crustacean (shellfish) allergies are reported in up to 2% of the population in the United States.²⁶ Glucosamine product labeling contains warnings against use in patients with crustacean allergies, due to potential contamination with crustacean allergens during the extraction process. Some studies have shown no

THE BOTTOM LINE

- Many patients report medication allergies. It is important to discern whether these are true allergies or simply an intolerance.
- In patients in which a true allergy exists, knowledge and selection of alternative therapies is crucial.
- Alternative therapy should consist of medications that are structurally different than the medication to which the patient is allergic.
- Documentation of allergic reactions, as well as medications to which the patient is not allergic, is important.

cross-sensitivity in shrimp-allergic patients, but this cannot be extrapolated due to a lack of standardization in the extraction process or between glucosamine products. Patients with a shellfish allergy who wish to use glucosamine products should confirm that the product manufacturer obtains glucosamine via a corn fermentation process, and not from shellfish.

MEDICAL MANAGEMENT OF HYPERSENSITIVITY REACTIONS

The medication implicated in an acute hypersensitivity reaction should always be discontinued. Treatment is based on severity, and may include antihistamines, corticosteroids, histamine (H₂) receptor antagonists (eg, ranitidine), and epinephrine.²⁷ However, premedication with antihistamines or corticosteroids is not effective in preventing severe hypersensitivity reactions in patients with true allergies. The causative medication, as well as the nature of the allergic reaction, should be documented in the medical record.

The patient should be advised to inform future prescribers of the allergic reaction.

Desensitization procedures are an option in patients who must receive a medication to which they are allergic. These procedures involve administering gradually increasing doses of the drug over hours to days to allow the patient to tolerate the medication. Desensitization should be performed in a facility where appropriate monitoring is possible and by a physician experienced with these procedures.²⁷ Contraindications to desensitization include Stevens-Johnson syndrome, toxic epidermal necrolysis, severe exfoliative dermatitis, or allergy-induced hepatitis. It is important to recall that desensitization does not create long-term tolerance to the medication.³ □

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