Pharmacy PRACTICE

continuing education lesson

Drug allergies: a review

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1 CEU

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Learning objectives

Upon successful completion of this lesson, you should be able to:

1. describe the risk factors associated with the development of an allergic reaction
2. explain the role of skin testing and desensitization in patients who develop a possible reaction to beta-lactam antibiotics
3. provide guidance for therapeutic alternatives for patients experiencing an allergic reaction to beta-lactam or sulfonamide antibiotics, ASA or NSAIDs

To successfully complete the post-test for this lesson, you may need access to the Compendium of Pharmaceuticals and Specialties (*CPS*).

An adverse drug reaction (ADR) has been defined by the World Health Organization as any noxious, unintended and undesired effect of a drug that occurs at doses used for prevention, diagnosis or treatment.[1] Although many patients and clinicians may refer to an ADR as an "allergic reaction," an allergic drug reaction is only one type of ADR.

Patients who develop an allergic drug reaction often have many questions and concerns including which drugs they need to avoid and which drugs they can safely take. As well, they may needlessly avoid taking necessary medications such as penicillin, because they mistakenly think they are allergic to the drug when they are not.

Pharmacists can provide valuable advice to these patients regarding allergic and pseudoallergic drug reactions. Beta-lactam antibiotics, sulfonamides and nonsteroidal anti-inflammatory drugs (NSAIDs) comprise 80 per cent of all reports of allergic reactions and pseudoallergic reactions.[2] This lesson will provide pharmacists with an understanding of drug allergies specifically related to beta-lactam and sulfonamide antibiotics, and ASA/NSAID reactions.

Epidemiology of drug-induced reactions

ADRs are a common phenomenon. Epidemiologic studies have shown that serious ADRs occur in 6.7 per cent of all hospitalized patients[3] and that three to six per cent of all hospital admissions are the result of ADRs.[4] The cost of drug-related morbidity and mortality has been estimated at more than $177 billion US a year,[5] and ADRs are thought to be between the fourth and sixth leading cause of death in the United States.[3]

ADRs are generally grouped into two categories: those that are predictable, common and related to the pharmacology of the drug, and those that are unpredictable, uncommon and are not related to the pharmacology of the drug (Table 1). Approximately 80 per cent of all ADRs are considered predictable; examples include side effects and drug interactions.[6]

Unpredictable reactions include drug intolerance (an undesired, unexpected effect produced by the drug at therapeutic or subtherapeutic dosages), idiosyncratic reactions (related to genetic susceptibilities or undefined mechanisms), and allergic (also known as immunologic or hypersensitivity) reactions.[6]

Allergic reactions caused by drugs are always associated with an immune mechanism, either drug-specific antibodies or activated T-lymphocytes. Pseudoallergic reactions (also known as anaphylactoid) differ from allergic reactions in that they are not immune-mediated, but are often the result of direct histamine release. Allergic reactions are often subdivided into four types according to a system proposed by Coombs and Gell (see Table 2).[7] Some drug-induced hypersensitivity reactions, such as bullous or pustular skin eruptions or hepatitis, do not seem to fit into the Coombs and Gell classi-

Instructions

1. After carefully reading this lesson, study each question and select the one answer you believe to be correct. Circle the appropriate letter on the attached reply card.
2. Indicate if you are already registered as an annual CE Club Member or if you would like to become a member.
3. Complete the card and mail, or fax to (416) 764-3937.
4. Your reply card will be marked and you will be advised of your results within six to eight weeks in a letter from Pharmacy Practice.
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TABLE 1 Classification of adverse drug reactions

Type of reaction		Example
Predictable (Type A)	Side effect	Erythromycin: gastrointestinal toxicity
	Secondary effect of drug	Clindamycin: *Clostridium difficile* pseudomembranous colitis
	Overdosage	Tricyclic antidepressants: cardiac arrhythmias
	Drug-drug interaction	Atorvastatin and erythromycin
Unpredictable (Type B)	Allergic (hypersensitivity, immunologic)	Penicillin: anaphylaxis
	Idiosyncratic	Sulfonamide antibiotics: toxic epidermal necrolysis
	Pseudoallergic	Radiocontrast media: anaphylactoid reaction
	Intolerance	ASA: tinnitus (usually with excessive doses)

TABLE 2 Four classic hypersensitivity reactions[7]

Type of reaction	Description	Primary effector mechanism	Clinical reaction	Onset
I	Anaphylactic or immediate-type hypersensitivity	Drug-specific IgE antibodies	Urticaria, hypotension, angioedema, bronchospasm, anaphylaxis	Minutes to hours after drug exposure
II	Cytotoxic	IgG or IgM antibodies	Hemolytic anemia	Variable
III	Immune complex reaction	Soluble immune complexes	Leukocytoclastic vasculitis	1-3 weeks after drug exposure
IV	Delayed or cell-mediated hypersensitivity	Sensitized T-lymphocytes	Contact dermatitis, fixed drug eruptions, exanthematous eruptions	3-10 days after drug exposure

fication. Some authors have divided the delayed hypersensitivity reactions (i.e., Type IV), into different subcategories such as Type IVa, IVb and IVc, which correspond to different T-cell subsets and functions.[7]

Immediate-type and delayed-type hypersensitivity reactions are more common than cytotoxic or immune-complex reactions.

There are several features that characterize an allergic reaction, including the following:[8]

- the reaction requires a period of sensitization, and does not generally occur on first exposure
- the reaction occurs at a dose much lower than that required for a pharmacologic effect
- clinical symptoms are characteristic of an allergic reaction
- resolution usually occurs within three to five days after discontinuation of the drug

Although the frequency of drug allergies has been difficult to determine, it is known that they comprise only a small proportion of all ADRs. Approximately 10-15 per cent of all ADRs are considered allergic reactions.[7] The most common allergic reactions involve the skin and are observed in approximately two to three per cent of hospitalized patients.[9] Skin eruptions are most commonly observed since the skin is the most visible organ.

Pathogenesis of allergic drug reactions

Large drug molecules, such as insulin and protamine, are intrinsically immunogenic (i.e., able to elicit an immune response). However, most drugs are smaller molecules, less than 1000 daltons, and are nonimmunogenic in their native state. In order to become immunogenic, the drugs must bind covalently to high-molecular weight carrier proteins and also undergo antigen processing; this simple chemical carrier complex is known as a hapten. Some drugs, such as penicillin, are chemically reactive due to the instability of their molecular structure. Other drugs, such as sulfonamide antibiotics, require metabolism to a reactive form before an immune response is initiated.[10]

Beta-lactam antibiotic allergies

Beta-lactam antibiotics, including penicillins, cephalosporins, monobactams and carbapenems, are one of the most widely used classes of antibiotics. Allergic reactions to beta-lactam antibiotics, especially penicillin, are not uncommon. Studies have shown that almost 20 per cent of the population considers themselves allergic to penicillins, although in fact less than 10 per cent of the population is truly

CE Faculty

This month

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All lessons are reviewed by three pharmacists for accuracy, currency and relevance to current pharmacy practice.

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allergic to penicillin.[11,12] In many cases, the patients consider any "adverse reaction" to penicillin (e.g., nausea, diarrhea, vaginitis) to be an "allergic" reaction. Penicillin is often withheld from many patients who could safely receive the drug or other beta-lactam antibiotics, perhaps affecting therapeutic outcomes.[13] The label of "penicillin allergy" can be removed based on history alone in up to 28 per cent of patients who consider themselves allergic.[11] Studies have shown that incorrectly labelling patients as penicillin-allergic was associated with increased healthcare costs.[14]

Allergic reactions to beta-lactam antibiotics encompass the entire spectrum of immunologic reactions, including anaphylaxis, urticaria, hemolytic anemia, interstitial nephritis, delayed exanthems (also known as maculopapular or morbilliform eruptions) and fixed drug eruptions. The most common beta-lactam-induced drug reactions are delayed exanthems that occur at least four to five days after therapy is initiated, and urticaria.

The reaction that most patients and clinicians fear is anaphylaxis. However, anaphylactic reactions to penicillins are very rare. Data from the 1960s suggested that the occurrence rate of penicillin-induced anaphylaxis was 1.5 to 4 cases per 10,000 treated patients.[15] More recent data indicate that the incidence rate of anaphylactic reactions to penicillin is 0.2 per cent,[16] with fatalities occurring in one to two of 100,000 treated.[17] Despite the rarity of cases, however, anaphylaxis is a very real concern. Approximately 75 per cent of fatal anaphylactic cases in the United States each year are attributed to penicillin.[18] Some patients may be extremely sensitive to penicillin. One report documents a systemic reaction in a penicillin-allergic patient after intercourse with a partner who had received dicloxacillin.[19]

Risk factors

Several factors have been identified that may increase the risk for the development of penicillin allergy. Prior exposure to penicillin or a related agent is required in order to stimulate the production of antigen-specific IgE. Therefore, patients do not develop a reaction on their first dose, but rather on repeat exposure to penicillin. It should be noted that prior sensitization can occur with a therapeutic course of penicillin or from environmental or occupational exposure (e.g., *in utero* exposure of a fetus, breast milk exposure, ingesting milk from penicillin-treated cows).[20] Allergic reactions are more likely to occur through the topical route, followed by injectable, and then oral administration.[21]

Although coincidental dual allergies may occur, a patient who is allergic to mold and whose skin test results are positive to the mold *Penicillium* is at no increased risk of penicillin allergy.[20] Young and middle-aged adults are at greatest risk for developing penicillin allergy, whereas children and the elderly may have reduced immune responses.[20] No genetic basis has been found for penicillin IgE-induced allergy. Certain major histocompatibility complex haplotypes seemed to be implicated in delayed hypersensitivity reactions, but not IgE-induced reactions, to aminopenicillins.[22] In addition, a history of atopy does not increase the risk for developing an allergic reaction to penicillin.[20] However, an atopic constitution may place sensitized individuals at increased risk for a severe anaphylactic reaction if penicillin-specific IgE antibodies are produced.[23]

Sex and race do not appear to be risk factors for the development of a penicillin allergy.[23] However, female gender has been identified as a potential risk for the development of adverse events. Several factors may explain the higher adverse event rate observed in female patients including pharmacokinetic and pharmacodynamic factors, hormonal influences, healthcare utilization, reporting bias and increased use of medications in women.[24]

Length of time since the reaction is an important consideration in determining skin test reactivity. Over time, there is a gradual but highly variable decline in the IgE concentration. One study revealed skin-test positivity in 80 to 90 per cent of patients within two months of an acute allergic reaction, which declined to less than 22 per cent at 10 years.[25]

Immunochemistry

The immunochemistry of penicillin has been well characterized, whereas the immunogenic determinants of the cephalosporins are still widely unknown.[26] All beta-lactam antibiotics contain a beta-lactam ring and a thiazolidine ring. Penicillin is intrinsically unstable; the beta-lactam ring opens, allowing the carbonyl group to form linkages with amino groups of lysine residues on nearby proteins.[27] This antigenic determinant (benzyl penicilloyl) is known as the "major determinant" because approximately 95 per cent of penicillin molecules bind in this way. The remainder of the metabolites of penicillin are known as "minor determinants" and consist of benzylpenicillin, its alkaline hydrolysis product (benzylpenicilloate) and its acid hydrolysis product (benzylpenilloate). Although these products comprise only a small percentage of the breakdown products of penicillin, they are not minor in terms of clinical reactivity. In fact, anaphylactic reactions are often mediated by IgE directed against the minor determinants.

Side chain groups on the beta-lactam antibiotics may also play a significant role in the development of immediate reactions and delayed reactions to this class of antibiotics. Penicillins have a thiazolidine ring and cephalosporins have a dihydrothiazine ring. Some penicillins and cephalosporins also share common side chains. Some examples of common side chains include penicillin G and cefamandole, cephalothin and cephaloridine, ampicillin and cephalexin, and amoxicillin and cefadroxil.[27,28] Cefazolin is unique in that its side chains are distinct from other penicillins and cephalosporins. There are numerous reports in the literature documenting patients who have developed an allergic reaction to a specific penicillin or cephalosporin but have good tolerance to other beta-lactam antibiotics.[29,30]

The immune determinants of the cephalosporins and carbapenems have not been well characterized. Although these compounds may also undergo spontaneous degradation of the beta-lactam ring, these intermediaries do not appear to be antigenic. The immune responses to the cephalosporins and carbapenems may be directed toward the side chains of the compound and not to the core ring structure.[31] One study showed that IgE-binding determinants on cefaclor encompassed the entire molecule.[32] Lack of knowledge of cephalosporin antigenic determinants has hindered our understanding of cross-reactivity between beta-lactam antibiotics.

Skin and patch testing

Penicillin skin testing, using both major and minor determinants, had been used for many years to evaluate penicillin allergic status. Skin testing is used primarily for determination of IgE-mediated reactions. Unfortunately, the minor determinant mixture (MDM) has never been commercially available in Canada, due to the marked instability of penilloate and penicilloate metabolites in solution.[17] As well, the major determinant is no longer commercially available in North America. This has severely hampered the use of penicillin skin testing to determine immune status of penicillin allergic patients. Many physicians test only with the major deter-

minant and penicillin G; however, this means that some patients at risk of potentially serious, anaphylactic reactions will be missed.

The positive predictive value of skin testing is unclear because patients with a convincing history of a Type I reaction to penicillin who subsequently react to skin testing are unlikely to undergo an oral penicillin challenge to confirm the allergy. The overall reaction rate in skin test-negative, history-positive patients was about one per cent for studies that used minor and major determinants.[17] The most common reaction observed was urticaria.[17]

The gold standard is considered to be the combination of negative penicillin skin testing followed by an oral penicillin challenge. The drug hypersensitivity practice parameter developed by the Joint Council of Allergy, Asthma and Immunology in the United States recommends a graded oral challenge, with an initial 1/100 test dose followed by the full therapeutic dose (if no reaction occurred during the brief observation period).[33] The patient is observed for a minimum of three hours following the full-dose challenge.

Patients who undergo skin testing should not take any antihistamines (e.g., loratadine, diphenhydramine, doxepin) for at least 48 hours or more before the procedure since this will interfere with the wheal and flare response. (A wheal and flare response is similar to what is produced by a mosquito bite. A small hive may form in the middle of a larger sized area of redness.) As well, beta-blockers should be discontinued whenever possible, since allergic reactions that may occur during skin testing may have increased severity and, more importantly, have a less effective response to standard anti-anaphylaxis treatment (i.e., epinephrine). Glucagon is recommended as an alternative treatment in management of anaphylaxis in these cases.[34]

Patch testing (i.e., topically applied), using the drug in a suitable concentration and vehicle, usually in petrolatum, is used to confirm various delayed Type IV reactions including contact dermatitis and delayed maculopapular rashes.[35] The overall sensitivity of patch testing is estimated to be 30 to 60 per cent, which means that a negative patch test does not exclude a hypersensitivity reaction.[36] Delayed reading intradermal skin testing is also used to help diagnose Type IV reactions, specifically delayed rashes. For standard skin testing for IgE-mediated reactions, the skin test site is observed after 15-20 minutes. For delayed reading intradermal skin testing, the skin test site is observed after 24 hours and up to 7 days after skin testing.

Aminopenicillin (ampicillin, amoxicillin) rashes

Delayed cutaneous eruptions, mostly in the form of maculopapular rashes, are not uncommonly associated with ampicillin or amoxicillin. They can appear two to three days after the drug is started, although they usually occur near the end of therapy (i.e., days 8 to 10). The incidence of these drug rashes during therapy has been estimated at 9.5 per cent.[37] Some delayed hypersensitivity reactions can be identified through patch or delayed reading intradermal skin tests. Cutaneous symptoms may be a manifestation of the underlying infection rather than an allergic reaction to the drug prescribed to treat the infection. For example, for patients administered ampicillin or amoxicillin, delayed skin eruptions develop in 60 to 100 per cent of those with a primary infection of Epstein-Barr virus (EPV) and possibly lymphocytic leukemia and cytomegalovirus. The rash is extensive, maculopapular and pruritic, and is usually accompanied by fever. Although the mechanism of the reaction has not been clarified, it does not appear to be IgE-mediated.[38]

Serum sickness-like reactions

Cefaclor has been associated with the development of a serum sickness-like reaction. This reaction is defined by fever, rash (usually urticarial) and arthralgias occurring one to three weeks after initiation of the drug.[39] Other symptoms, such as lymphadenopathy and eosinophilia, may also be present. In contrast to true serum sickness, serum sickness-like reactions such as those found with cefaclor are not associated with immune complexes, hypocomplementemia, vasculitis and renal lesions. The overall frequency of cefaclor-induced serum sickness-like reaction has been estimated at 0.024 to 0.2 per cent per course of cefaclor prescribed.[40] Evidence indicates that in genetically susceptible hosts, a reactive cefaclor metabolite is generated during its metabolism that may bind with tissue proteins and elicit an inflammatory response manifesting as serum sickness-like reaction.[41] For cefaclor, the risk of cross-reaction with beta-lactam antibiotics is small, and the administration of another cephalosporin is usually well tolerated.[40] However, some clinicians recommend avoidance of all beta-lactams in patients who experienced a serum sickness-like reaction due to cefaclor.[42]

Desensitization

Desensitization refers to the process of creating immunologic tolerance to an antigen against which specific IgE antibodies are present. For rapid drug desensitization, progressively increasing doses of the sensitizing drug are administered over the course of several hours to produce a state that allows safe treatment with the medication. Although desensitization is classically used for IgE-mediated reactions, it has also been used for non-IgE-mediated drug reactions including ASA (acetylsalicylic acid) desensitization and sulfonamide desensitization.[43]

Desensitization should be considered only when treatment with an alternative class of antibiotics is not feasible. For example, penicillin is recommended for treatment of syphilis during pregnancy, since erythromycin and clindamycin are less efficacious and may not cross the placenta in sufficient quantities. Penicillin desensitization is also indicated in patients with a positive history of penicillin allergy in whom skin testing cannot be done (for example, due to the unavailability of major and minor determinants in Canada). For penicillin, desensitization does not prevent non-IgE-mediated allergic reactions, such as a delayed maculopapular rash. As well, patients with a history of severe penicillin-induced reaction (such as Stevens-Johnson syndrome, toxic epidermal necrolysis or interstitial nephritis) should not receive the drug under any circumstance.[43]

Starting doses for penicillin desensitization are approximately 1/10,000 of the therapeutic dose. Oral desensitization protocols are recommended, whenever feasible. Doubling doses are administered every 15 minutes until the full dose is reached. Penicillin desensitization does not necessarily prevent a reaction from occurring but it does reduce the risk of anaphylaxis. Mild systemic reactions have been reported in about one-third of patients (usually urticaria), but no fatal or life-threatening reactions have been reported. Pre-medication with antihistamines or corticosteroids is not recommended since they are not effective in preventing severe reactions, and in fact may mask some early warning signs of an impending reaction. The oral, rather than the parenteral, route has been advocated due to the lower cost, increased convenience and safety associated with the oral route.[43]

Upon successful completion of the desensitization regimen, the patient is considered "desensitized" only for the course of therapy, which should begin immediately following the

procedure. Skin testing to penicillin is usually negative immediately after desensitization. If there is a lapse in therapy or the patient requires any beta-lactam at some point in the future, the patient must be assumed to be allergic and similar precautions taken.[43]

Cross-reactivity amongst beta-lactam antibiotics

The overall rate of cross-reactivity is unknown. Initial studies reported extremely high rates of cross-reactivity in the order of eight to 18 per cent in patients with a history of penicillin allergy who were subsequently challenged with cephalothin.[44,45] However, these data are fraught with potential biases. Early preparations of cephalosporins contained trace amounts of penicillin in solution, estimated to be 0.05 units of penicillin per gram of cephalothin.[26] Although the significance of this contamination is unknown, this further complicates the information available on cross-reactivity. As well, a patient-reported history of penicillin allergy is often unreliable.[11] Many of the early reports were based solely on the patient's recollection, not on skin testing results. Therefore, an actual allergy could not be confirmed, and non-IgE reactions may have been grouped together with IgE-mediated reactions.[46,47] There may be a three-fold higher risk of penicillin reactions in patients with a history of an adverse drug reaction from an unrelated medication.[46,47]

The immunogenic determinants of cephalosporins are unknown. This lack of information makes it difficult to develop skin test material for cephalosporins. Studies have suggested that most antibodies are directed towards the side chains of the cephalosporins.[26] This would imply that cross-reactions occur mostly between cephalosporins that share the same or similar side chain as the penicillins to which the patient reacted. Some of the first-generation cephalosporins, such as cephalothin and cephaloridine, have similar side chains to benzylpenicillin. Therefore, some of the early data that suggested a relatively high rate of cross-reactivity among the beta-lactam antibiotics may have been the result of side chain reactions.[48] Clinical cross-reaction is rare between penicillins and second- and third-generation cephalosporins.[26]

Carbapenems (e.g., imipenem, meropenem) should be considered potentially cross-reactive with beta-lactam antibiotics. A retrospective analysis determined that the incidence of an allergic-type reaction to a carbapenem was 11 per cent in patients with a reported or documented penicillin allergy; this rate was 5.2 times greater than the risk in patients who were not allergic to penicillin.[49]

Guidelines

In patients with a history of penicillin allergy who require a beta-lactam drug, the following recommendations have been made:[50]

1. A careful history is of vital importance. One of the key questions is whether the patient has tolerated a beta-lactam drug at any point since the time of the reaction. Information obtained regarding beta-lactam administration prior to the reaction is of no consequence. It is important to determine which beta-lactam antibiotic the patient had the reaction to, as well as the onset of the reaction in relationship to starting the medication. As well, non-IgE-mediated reactions (such as delayed maculopapular rashes) would not generally be identified through skin testing. Patients who develop a nonspecific rash while taking beta-lactams should not be automatically labelled as penicillin-allergic without considering other possibilities, such as a viral-induced skin eruption. Although there is a lack of data to suggest that other beta-lactam medications should be avoided, any patient with a serious adverse drug reaction (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis, nephritis) that may be due to penicillin should avoid the use of the implicated drug as well as other beta-lactam medications.
2. Although skin testing is recommended, it does not identify all types of allergies. As well, this option is not viable in most centres across Canada due to the commercial unavailability of the major and minor determinants. With any negative skin testing procedure, a graded oral challenge or small test dose (1/100th to 1/10th of full therapeutic dose) should be given.
3. When skin testing is not available, avoidance of cephalosporins is suggested in patients with an IgE-mediated reaction to penicillin (e.g., urticaria, anaphylaxis). In patients with a delayed rash to penicillin, especially if it occurred many years ago, use of a cephalosporin drug could be cautiously attempted.[50]

Sulfonamide allergies

The term sulfonamide is used to describe any compound with an SO_2NH_2 moiety. The major difference between sulfonamide antimicrobials and other sulfonamide-containing medications, such as furosemide, thiazide diuretics, acetazolamide and celecoxib, is that sulfonamide antimicrobials contain an aromatic amine group at the N4 position (Table 3). In addition, sulfonamide antimicrobials also contain a 5- or 6-member aromatic heterocyclic ring; this substituted ring is not found with non-antibiotic sulfonamides. "Sulfa" allergy is a generic term used to describe patients with allergies to sulfonamide antimicrobials. It does not imply allergy to compounds containing sulfur, inorganic sulfate or sulfite.[51]

TABLE 3 Examples of antibiotic and non-antibiotic sulfonamides

Antibiotic sulfonamides	Sulfamethoxazole Sulfisoxazole Sulfadiazine Sulfacetamide
Non-antibiotic sulfonamides	Acetazolamide Bumetanide Celecoxib Chlorothiazide Chlorpropamide Dorzolamide Furosemide Glyburide Hydrochlorothiazide Valdecoxib

Immunological reactions caused by sulfonamide antimicrobials encompass the entire spectrum including urticaria and anaphylaxis (Type I reaction), immune thrombocytopenia (Type II reaction), vasculitis (Type III reaction) and fixed drug eruptions and maculopapular eruptions (Type IV reaction). Approximately three per cent of patients in the general population have hypersensitivity reactions to sulfonamide antimicrobials.[52] For Type I reactions, the substituted heterocyclic ring, and not the SO_2NH_2 group, has been found to direct specificity to IgE-antibodies.[53] Idiosyncratic reactions, such as serum sickness-like reactions, hypersensitivity syndrome reaction and serious dermatologic reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis), are also associated with sulfonamide antimicrobials. Up to 60 per cent of HIV-infected patients experience trimethoprim-sulfamethoxazole (TMP-SMX) adverse reactions during therapy.[54]

The *hypersensitivity syndrome reaction* is a complex drug reaction that affects various organ systems. This potentially life-threatening syndrome is signaled by a triad of fever, skin eruption and internal organ involvement (usually

liver) that usually occurs on first exposure to the drug two to eight weeks after the initiation of therapy. Fever often precedes the development of the skin eruption by approximately one day. It occurs in approximately one in 1,000 to one in 10,000 exposures to such agents as aromatic anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine), lamotrigine, sulfonamide antibiotics and allopurinol. For sulfonamide antibiotics, the aromatic amine group is considered to be critical in the development of idiosyncratic reactions, including the hypersensitivity syndrome reaction.[55] This group is absent in the structure of non-antibiotic sulfonamides.

Skin testing

Skin testing with sulfonamide antibiotics has not been validated. *In vitro* tests, such as the lymphocyte toxicity assay, are available only for research purposes. For patients who may have developed an allergic reaction (e.g., anaphylaxis or delayed maculopapular rash), avoidance of all sulfonamide antibiotics is often recommended.

Cross-reactivity

Cross-reactivity between various sulfonamide-containing medications, namely antibiotics and non-antibiotics, has not been substantiated in the literature. For sulfonamide antimicrobials, the sulfonamide moiety (i.e., SO_2NH_2) itself does not trigger serious drug reactions such as the hypersensitivity syndrome reaction, nor IgE-mediated reactions. Non-aromatic amine sulfonamides, such as furosemide, hydrochlorothiazide, celecoxib and acetazolamide, would not be expected to clinically cross-react with sulfonamide antimicrobials.[46,56,57] Patients who experience an idiosyncratic drug reaction with a sulfonamide antimicrobial should avoid all sulfonamide antimicrobials. Although clinical data are lacking, patients should also avoid other aromatic amines such as procainamide, dapsone and acebutolol.[39] For patients who experience an IgE-mediated reaction, avoidance of sulfonamide antimicrobials is suggested. There is no evidence that patients who develop allergic or idiosyncratic reactions to sulfonamide antimicrobials need to avoid non-antibiotic sulfonamides.[46,51,57]

Desensitization

For patients who require a sulfonamide antibiotic, desensitization is an option. For example, TMP-SMX is the drug of choice for patients, including HIV-infected patients, infected with *Pneumocystis carinii*. A number of TMP-SMX desensitization protocols have been studied, especially in HIV-infected patients.[54] The protocols varied in terms of the starting dose of TMP-SMX (1 nanogram to 4 milligrams), the incremental increase between doses, the time interval between doses, and the total duration of the desensitization (five hours to 33 days).[43]

ASA and NSAID allergies

Adverse drug reactions to ASA and NSAIDs are not uncommon. Most ADRs resulting from the use of these drugs are predictable Type A reactions, such as gastrointestinal effects. However, ASA and NSAIDs that preferentially inhibit cyclooxygenase (COX)-1 can also induce three other types of reactions: bronchospasm with rhinoconjunctivitis, urticaria/angioedema and anaphylaxis.[58]

Respiratory reactions are often manifested as rhinorrhea and nasal congestion, paranasal head pain, conjunctivitis, periorbital edema, laryngospasm and asthma. The onset of susceptibility to the reaction usually occurs around 30 years of age, and is more prevalent in patients with allergic rhinitis and asthma. Approximately 20 per cent of patients with asthma and 20 per cent of patients with nasal polyps experience respiratory reactions following ASA and traditional NSAIDs.[59] Bronchoconstriction usually appears within 15 to 30 minutes after ingestion, although it may be delayed up to three hours.[58] Approximately one-third of patients with chronic idiopathic urticaria will experience a flare of urticaria after ingesting ASA or one of the older NSAIDs.[60]

The mechanism for ASA-exacerbated respiratory disease and ASA-induced urticaria/angioedema is not an IgE-mediated reaction; rather, it is believed to be related to the inhibition of COX-1. Prostaglandin E2 (PGE2) is depleted by the inhibition of COX-1, allowing synthesis of new leukotrienes and release of histamine from mast cells.

IgE-mediated anaphylaxis and urticaria/angioedema reactions can also rarely occur to NSAIDs. In contrast to prostaglandin-mediated reactions, prior sensitization is essential for IgE-mediated reactions. As well, patients only react to the drug to which they have been sensitized[61] and cross-sensitivity is not a concern.

Cross-reactivity

Cross-reactions between ASA and traditional NSAIDs (i.e., those that inhibit COX-1 enzyme such as ibuprofen, naproxen, diclofenac and ketorolac) are well documented, especially for patients with histories of respiratory reactions. Patients with non-IgE urticaria/angioedema may develop cross-reactions with ASA and traditional NSAIDs, although some studies suggest that cross-reactions may not always occur, except in patients with chronic idiopathic urticaria.[58] Acetaminophen and salsalate (the latter being no longer available in Canada) are poor inhibitors of COX-1; at higher doses (acetaminophen 1000 mg or greater, salsalate 2000 mg), these agents may also induce respiratory and cutaneous reactions in susceptible patients.[62] Similarly, meloxicam at low doses (e.g., 7.5 mg daily) does not induce cross-reactions. However, as the dose increases, cross-reactions may occur with COX-1 NSAIDs and ASA.[58]

In patients with ASA-induced respiratory reactions, COX-2 inhibitors have been well tolerated. Specifically, rofecoxib (no longer available) and celecoxib have been studied.[63-65] Despite evidence showing that celecoxib is well-tolerated in patients with ASA-induced respiratory reactions, the product monograph has not been changed to reflect this new scientific data. The celecoxib monograph still indicates that celecoxib is contraindicated in patients who have experienced asthma, urticaria or allergic type reactions after taking ASA or other NSAIDs. Challenge studies with valdecoxib are needed before it can be recommended for use in patients with ASA-induced respiratory disease.

Desensitization

Skin testing is not useful in patients with ASA-induced respiratory disease or urticaria; as well, skin testing is not used for patients with presumed IgE-mediated reactions, since testing has not been validated. Desensitization is an option for patients with ASA-induced respiratory disease in whom ASA is considered essential therapy. It does not appear to be useful in patients with skin reactions to ASA. Various desensitization protocols have been used, including incremental doses of ASA given over a 48-hour period until a dose of 650 mg is tolerated without a reaction. Patients must remain on ASA chronically; if ASA is discontinued for more than one day, it may be necessary to restart the entire desensitization protocol. Since cross-sensitization between ASA and the NSAIDs occurs, patients can be desensitized to ASA and then switched over to an NSAID.[58]

Conclusion

Adverse drug reactions are a common problem, and approximately 10-15 per cent of these

events are allergic in nature. Pharmacists are in a unique position to evaluate patients who may have developed an allergic reaction as well as provide guidance regarding avoidance of future incidents.

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Questions

1 All of the following statements about allergic reactions are true *except:*

a) The antibodies involved in allergic reactions are IgG, IgM and IgE.
b) Sensitization must occur prior to the development of an allergic reaction.
c) Allergic reactions generally subside within 14-28 days after discontinuation of the offending drug.
d) Symptoms characteristic of an allergic reaction include urticaria, shortness of breath and angioedema.

2 Which of the following patients would be *least* likely to suffer an allergic drug reaction?

a) an elderly woman with a history of hypertension
b) a new mother who was treated with cephalosporins during labour
c) a young adult with a history of urticaria and angioedema following penicillin, who was administered penicillin again
d) an HIV-infected patient receiving trimethoprim/sulfamethoxazole for *Pneumocystis carinii* pneumonia

3 Which of the following statements is true regarding desensitization?

a) It is important to give antihistamines and corticosteroids prior to the desensitization.
b) Desensitization provides lifelong immunogenic protection for the patient, regardless of whether the drug is discontinued.
c) Skin testing to penicillin is often positive immediately following desensitization.
d) Desensitization to trimethoprim/sulfamethoxazole may be preferred in HIV-infected patients who require therapy for *Pneumocystis carinii* pneumonia.

Questions

4 Which of the following is true regarding adverse drug reactions?
a) Adverse drug reactions occur in approximately 50 per cent of hospitalized patients.
b) Adverse drug reactions are often classified as either idiosyncratic reactions or side effects.
c) Adverse drug reactions are considered the fourth to sixth leading cause of death in the United States.
d) Patients who experience an adverse drug reaction should always avoid the use of the causative drug in the future.

5 Which of the following is true regarding predictable and unpredictable adverse drug reactions?
a) An example of an unpredictable reaction is nausea and vomiting associated with narcotic analgesics.
b) Dry mouth associated with amitriptyline is considered an unpredictable reaction, since it is not thought to be related to the pharmacology of the drug.
c) Approximately 40 per cent of all adverse drug reactions are considered predictable reactions.
d) Predictable reactions are dose-related, such as bleeding caused by excessive doses of warfarin.

Case A
A seven-year-old boy developed urticaria and shortness of breath three days after starting amoxicillin for treatment of otitis media. He had received amoxicillin in the past without any reaction. He has a history of asthma and eczema. He was positive on skin testing to the Penicillium *mold.*

6 Which of the following may have increased this patient's risk for developing a reaction?
a) age
b) prior use of amoxicillin
c) positive skin test to *Penicillium* mold
d) history of asthma and eczema

7 The patient is scheduled for penicillin skin testing. Which of the following medications should be discontinued prior to testing?
a) salbutamol inhaler
b) corticosteroid inhaler
c) loratadine
d) hydrocortisone cream

8 The results of the penicillin skin test and amoxicillin oral challenge are negative. Which of the following medications should the patient avoid in the future?
a) penicillin c) amoxicillin
b) cefprozil d) none of the above

9 Which of the following is *false* regarding serum sickness-like reactions?
a) Symptoms associated with serum sickness-like reactions include fever, skin eruption (usually urticaria) and arthralgias.
b) Immune complexes and renal involvement are commonly found in patients with serum sickness-like reaction.
c) Patients who develop serum sickness-like reaction from cefaclor should avoid cefaclor in the future.
d) Serum sickness-like reactions usually develop within one to three weeks after starting a medication.

10 A 35-year-old woman thinks that she may be "allergic to penicillin." She has never taken any beta-lactam antibiotics but her mother developed a severe reaction to penicillin and "almost died." Which of the following is true for this patient?
a) She should avoid penicillin, although she could take cephalosporins.
b) She should avoid all beta-lactam antibiotics.
c) She can safely take beta-lactam antibiotics, although her children may be at a greater risk for allergic reactions to this group of medications.
d) She can take any beta-lactam antibiotic, including penicillins and cephalosporins.

Case B
A 50-year-old man was prescribed trimethoprim-sulfamethoxazole for four weeks for treatment of chronic prostatitis. After two weeks, he developed a fever and maculopapular rash.

11 Which of the following is *false* regarding hypersensitivity syndrome reaction?
a) It most frequently occurs with sulfonamide antibiotics, anticonvulsants (phenytoin, phenobarbital, carbamazepine, lamotrigine) and allopurinol.
b) It usually occurs within two to five days after starting the drug.
c) Symptoms include fever, rash and internal organ involvement.
d) It occurs in approximately one in 1,000 to one in 10,000 administrations of TMP-SMX.

12 Which medications should this patient avoid in the future?
a) acetazolamide c) glyburide
b) propafenone d) dapsone

13 Which of the following medications is *not* a sulfonamide medication?
a) glyburide c) dorzolamide
b) valdecoxib d) magnesium sulfate

14 A 26-year-old man with infectious mononucleosis was prescribed amoxicillin and developed nonspecific rash seven days into the course of therapy. Which of the following drugs should he avoid in the future when he no longer has infectious mononucleosis?
a) ampicillin c) cefaclor
b) penicillin d) none of the above

15 A 25-year-old woman developed urticaria following the use of trimethoprim-sulfamethoxazole for the treatment of a urinary tract infection. Which of the following drugs should she avoid in the future?
a) glyburide
b) silver sulfadiazine cream
c) hydrochlorothiazide
d) acetazolamide

16 A 45-year-old woman has a history of a delayed rash to penicillin that occurred when she was a child. Which of the following medications should she avoid?
a) penicillin c) cefazolin
b) cefaclor d) all of the above

17 Which of the following is true regarding patch testing?
a) Patch testing is used for confirmation of Type II and Type III reactions (e.g., hemolytic anemia).
b) The overall sensitivity of patch testing is estimated to be approximately 90 per cent.
c) Patch testing is a topically applied test using the drug in an appropriate vehicle, such as petrolatum.
d) Patch testing should never be done in patients with a history of a delayed maculopapular rash.

Case C
A 65-year-old woman requires the use of an NSAID for her osteoarthritis. She has a history of bronchoconstriction 20 minutes after ASA ingestion. Her past medical history includes asthma, hypertension, osteoarthritis, nasal polyps and hypothyroidism.

18 What are risk factors for the development of ASA-induced respiratory disease for this patient?
a) her age
b) history of asthma
c) history of hypothyroidism
d) history of hypertension

19 What options are available for this patient for treatment of her osteoarthritis?
a) acetaminophen 1 g every six hours
b) naproxen 250 mg twice daily
c) celecoxib 200 mg once daily
d) ketorolac 10 mg every six hours

20 A 55-year-old man requires the use of ASA for cardiovascular prophylaxis. He has a history of wheezing, shortness of breath and rhinitis following ASA use. Of the following choices, what is the best choice for this patient?
a) valdecoxib c) ASA desensitization
b) diclofenac d) None of the above

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