

Hypersensitivity Reactions to Non-Beta-Lactam Antibiotics

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Abstract

As alternatives to beta lactam antibiotics continue to be developed, an increasing number of patients are experiencing hypersensitivity reactions to these agents. Unfortunately, unlike penicillin, there are no validated skin testing reagents to aid in confirming the presence of specific IgE antibodies to these drugs. This review summarizes what is known about hypersensitivity reactions to non-beta lactam antibiotics, and includes practical approaches to readministering these drugs in selected situations. Sulfonamides, vancomycin, macrolides, tetracyclines, fluoroquinolones, and anti-virals are included in the discussion.

Index Entries:

Sulfonamides; vancomycin; macrolides; tetracyclines; fluoroquinolones; anti-virals.

Introduction

Adverse drug reactions are frequent and potentially life-threatening occurrences. A recent meta-analysis of adverse drug reactions in hospitalized patients estimated an incidence of 6.7% and a fatality rate of 0.32% (1). Hypersensitivity reactions to medications are reported to account for 6–10% of inpatient ADRs, and of these, fatalities occur in 1 of 10,000 (2). Antibiotics are one of the most frequently prescribed

classes of medications, and their percentage of total spending is growing. A recent study from Scotland showed an increase of almost 50% in the percentage of total drug cost over just 5 yr (3). Non-beta-lactam antibiotics are being used in increasing numbers, and accordingly, we will see more and more unpredictable adverse reactions to these agents. Unfortunately, with the exception of reactions to sulfamethoxazole, our understanding of the pathophysiology of hypersensitivity reactions to non-beta-lactam antibiotics is incomplete.

A useful classification scheme has been developed for categorizing adverse drug reactions (4) (see Table 1). The first category is

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Table 1
Classification of Adverse Drug Reactions*

Type A: Common and Predictable Adverse Reactions	
I.	Effects of overdosage: e.g., seizures secondary to theophylline
II.	Adverse effects: immediate or delayed: e.g., sedation with antihistamines
III.	Secondary or indirect effects
	A. Related to drug alone: e.g., diarrhea from disturbance of bacterial flora
	B. Related to both disease and drug: e.g., maculopapular rash to ampicillin with viral infections
IV.	Interactions between/among drugs: e.g., bleeding with simultaneous use of warfarin and cimetidine
Type B: Uncommon and Unpredictable Adverse Reactions	
I.	Intolerance: e.g., tinnitus caused by small doses of aspirin
II.	Idiosyncratic reaction: e.g., warfarin-induced skin necrosis with protein C deficiency
III.	Hypersensitivity (immunologic) reactions: e.g., anaphylaxis to penicillin or radiocontrast media

*Adapted from deShazo and Kemp (2).

devoted to common and predictable reactions, and most reactions are in this category. It includes overdosage, direct or indirect effects, and drug interactions. The second and smaller category is designated “uncommon and unpredictable,” and includes intolerance, idiosyncratic, and hypersensitivity reactions. Several of these types of reactions may be life-threatening, but only hypersensitivity reactions involve immunologic sensitization and resultant highly specific effector responses by lymphocytes and/or antibodies. Although this classification is simple in theory, it is often difficult to use in real-world medical practice, especially with the less common adverse drug reactions. This is partly because it is often very difficult to determine the precise mechanism of an adverse drug reaction, including simply determining whether it involved immunologic hypersensitivity (5). For example, the antibiotic cefaclor can cause a classic serum-sickness presentation, implying an IgG- or IgM-mediated immune-complex mechanism. However, further study has shown that this reaction is caused by a direct cytotoxic effect of cefaclor metabolites in susceptible individuals (6). Thus, although the focus of this article is hypersensitivity reactions, in which the mechanism is unclear, other rare adverse drug reactions are included.

Testing

As with most pharmaceuticals, antibiotics are small, nonproteinaceous molecules that are incapable of activating the immune system by themselves. Instead, the drug or its metabolite (hapten) must bind an endogenous protein (carrier) before becoming immunogenic (*see* Fig. 1). The molecular immunology has been extensively studied for immediate hypersensitivity reactions to penicillin, and as a result a panel of penicillin skin-testing reagents has been developed that has excellent diagnostic utility. Unfortunately, technical limitations have thus far prevented the development of validated diagnostic testing reagents for the non-beta-lactam antibiotics (5,7). Instead, we must rely on the combination of a detailed clinical history, skin testing with questionable reagents, and challenge testing in the form of either a single test dose or a more formal graded challenge.

Skin Testing

As mentioned previously, there are no validated skin-testing reagents for the non-beta-lactam antibiotics. However, it can be presumed that the risk of an immediate hypersensitivity reaction would be high when there is a positive skin test to a nonirritative concen-

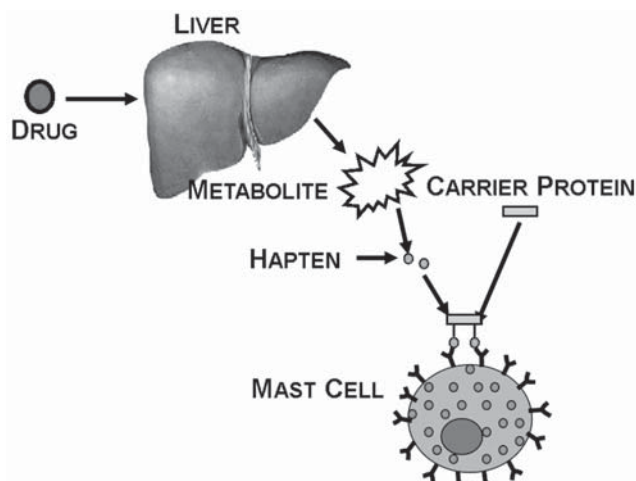


Fig. 1. A non-protein drug (or its reactive metabolite formed by hepatic or other processes) typically must bind as a hapten to an endogenous protein (carrier) before becoming immunogenic.

tration of the antibiotic in question (8). However, a negative skin test with a non-beta-lactam antibiotic is generally not helpful because a patient may be at risk for a reaction against a drug metabolite for which skin testing reagents are not available.

Desensitization and Challenge Testing

It is sometimes necessary or at least highly desirable to use a specific antibiotic in a given situation. For example, trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for patients with *Pneumocystis carinii*. Similarly, vancomycin is typically used to treat methicillin-resistant *Staphylococcus aureus*. The serious nature of these clinical indications combined with the absence of convenient alternative treatments may result in a risk-benefit ratio favoring a careful attempt to use the medication despite a history of a prior reaction. However, certain adverse-reaction histories are considered absolute contraindications to reintroducing the drug. These include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), severe exfoliative dermatitis, or hepatitis (9). A reaction history that suggests of mast-cell activation is generally best-suited for desensitization.

Greenberger separates desensitization protocols into two categories, true immunologic desensitization and test dosing (9). True immunologic desensitization leads to the temporary disappearance of skin and serum anti-medication IgE antibodies. This method is most appropriate for medications that can be tested in the patient to determine whether or not there is a true allergy, such as penicillins, or when skin tests are positive for nonirritating concentrations of a non-beta-lactam antibiotic. When skin testing is not done, or when it is negative for a non-beta-lactam antibiotic, a test-dosing protocol should be used. Both desensitization and test dosing involve the progressive administration of increasing doses of the offending medication. Because it can be difficult to make a distinction between some desensitization and test-dosing protocols, national practice guidelines have suggested that the more generic term "graded challenge" be applied (10). Protocols for test dosing of several drugs (including sulfonamides and vancomycin) have been published (11–14), but should always be undertaken with the consultation and supervision of a specialist trained in this area. Test-dosing and desensitization does not provide prolonged tolerance to the medication. Thus, the protocols must be repeated with subsequent courses of therapy.

Types of Non-Beta Lactam Antibiotics and ADRs

Sulfonamides

The sulfonamides were the first class of antibiotics introduced, and they still have a broad range of indications, including infections of the urinary, respiratory, and gastrointestinal (GI) tracts. TMP-SMX is the most widely used sulfonamide antibiotic. Among hospitalized patients, adverse reactions to TMP-SMX occur 8% of the time, usually involving the skin and GI tract (15). Approximately 3% of adverse reactions to TMP-SMX probably represent sulfonamide hypersensitivity reactions (16),

although life-threatening reactions to TMP-SMX are rare. The classic reaction consists of fever, maculopapular rash, and toxicity of one or more internal organs that develops 1–2 wk after therapy is initiated (21). Sulfonamides account for the largest percentage of the 10 cases per million persons per yr of antibiotic-induced TEN and Stevens-Johnson syndrome (22). Anaphylactic (21) and anaphylactoid reactions are rare, but have also been reported.

Adverse reactions to sulfonamides are very common in patients with human immunodeficiency virus (HIV), with a reported incidence of 60% (16) causing drug discontinuation 34% of the time (17). Fixed drug eruptions are the most common type of reaction, but erythema multiforme, TEN, Stevens-Johnson syndrome, and anaphylactoid reactions have also been reported (18). Additionally, a “hypersensitivity syndrome” characterized by hypotension, fever, rash, and pulmonary infiltrates has been described, and usually resolves with supportive therapy.

As discussed in the introduction, metabolism and haptenization are vital for many drugs to cause an allergic reaction. In the case of sulfonamides, oxidation of the arylamine group to form hydroxylamine determinants is important in forming the haptenated structure (19). It has also been shown that the substituted sulfonamide region plays a role in immune reactions (20) (see Fig. 2). Because not all medications with sulfa moieties share these characteristics, cross-allergenicity is rare.

The use of sulfonamide antibiotics has been to some degree supplanted by newer antibiotic classes because of emerging resistance patterns, sulfonamide side effects, and the marketing efforts of the manufacturers of newer antibiotics with patent protection. For the average patient who reports an adverse reaction to sulfa, it is usually acceptable to substitute a different antibiotic class for a particular infection. However, this practice is not necessary for most patients with HIV. TMP-SMX is the best antibiotic for *Pneumocystis carinii* pneumonia

(PCP) infection, PCP prophylaxis, and toxoplasmosis prophylaxis. Although there is no clinically proven method for testing a patient for sulfonamide hypersensitivity, desensitization protocols have been developed (11,12) for use in immune-compromised patients. Using a desensitization protocol, the vast majority of HIV patients with prior TMP-SMX hypersensitivity can be safely treated (see Table 2).

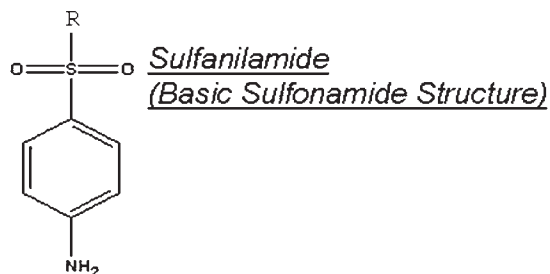
Vancomycin

Vancomycin is the mainstay—and until recently, the only—antibiotic for treating methicillin-resistant *Staphylococcus aureus*. Adverse reactions to vancomycin are common, but true hypersensitivity to it is rare. The most common limiting reaction to the drug is “red man syndrome,” which is generally believed to be caused by the drug’s direct action on mast cells resulting in histamine release (13). This anaphylactoid reaction does not require prior sensitization, and is often largely dependent on the rate of administration of the drug. TEN has been reported as well (23). In one small case series of seven patients who developed dose-limiting reactions to vancomycin, 100% had pruritus, 71% had flushing/erythema and/or urticaria, and 29% had hypotension (14).

Skin-testing for vancomycin allergies has been undertaken (13) to identify the rare presence of specific IgE to vancomycin. In most cases, vancomycin can be successfully administered to patients with prior histamine-mediated reactions by reducing the infusion rate and pretreating with H1 antihistamines. A “desensitization” protocol may also be employed with H1 antihistamines and glucocorticoids used as adjuncts in this process (see Table 3).

Macrolides

Erythromycin, azithromycin, and clarithromycin are members of the macrolide class of antibiotics. They are generally well-tolerated, although there is relatively high rate of GI-related side effects (25). Hypersensitivity reactions, usually characterized by rash, fever,



Structures of Sulfonamide Antimicrobials (All Contain an Arylamine Group)

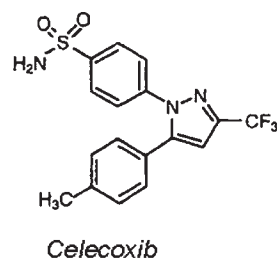
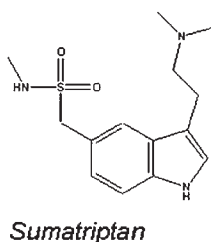
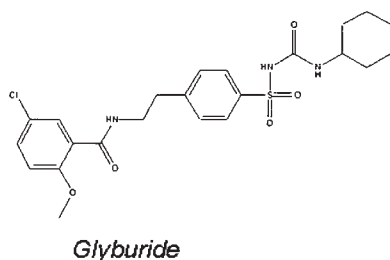
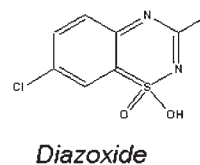
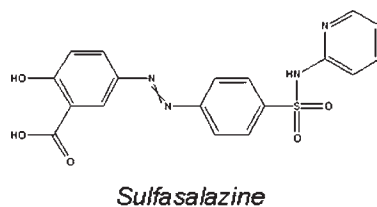
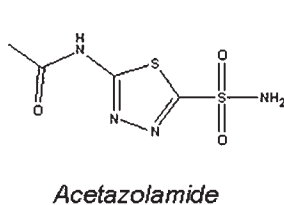
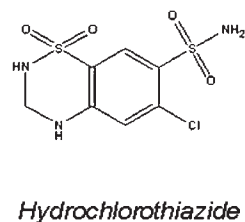
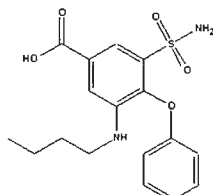
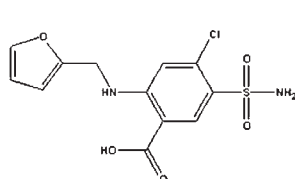
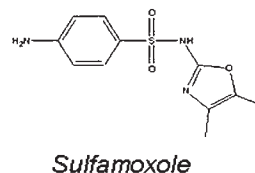
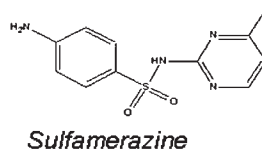
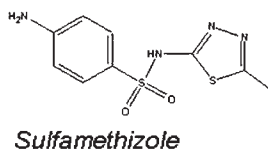
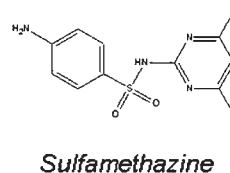
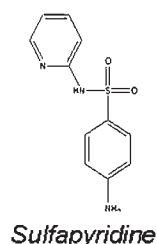
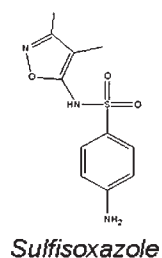
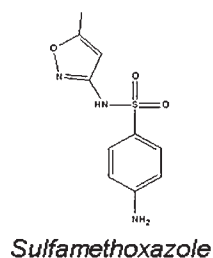


Fig. 2. Sulfanamide and structurally related drugs.

Table 2
TMP-SMX Desensitization Protocol*

	TMP (mg)	SMX (mg) PO
Day 1		
9 AM	0.8	4
11 AM	1.6	8
1 PM	4	20
5 PM	8	40
Day 2		
9 AM	16	80
3 PM	32	170
9 PM	40	200
Day 3		
AM	80	400

*Adapted from Montanaro (17).

eosinophilia, and/or joint pain, have been described. Serious reactions such as anaphylaxis (30) and Stevens-Johnson syndrome have also been reported, but are rare. Cholestatic hepatotoxicity is a well-known reaction to erythromycin, and has been reported for the other macrolides. This reaction is usually not believed to be allergic in nature, although one case report documented serum antibodies to erythromycin haptens (26). Skin testing has been performed (27), but has not been a useful diagnostic tool.

Tetracyclines

The tetracycline class of antibiotics consists of tetracycline, doxycycline, and minocycline. The utilization of this antibiotic class is somewhat unusual because it is commonly prescribed for weeks or months of continuous use to control acne vulgaris in otherwise healthy subjects. Common dose-dependent adverse reactions include photosensitivity and GI-related symptoms (28). Urticaria has been reported, although more widespread anaphylactic symptoms are very rare. Each of the tetracyclines has also been implicated on rare occasions with a hypersensitivity syndrome (consisting of fever, rash, and internal organ dysfunction), as well as a serum sickness-like reaction. Drug-

induced lupus has been attributed to minocycline (29), but not tetracycline or doxycycline. In one study reporting 32 cases of drug-induced lupus attributed to minocycline, the average interval of continuous treatment prior to the onset of adverse symptoms was 632 d (28). Although the pathophysiology of each of these adverse reaction types has not been fully determined, immunologic sensitization probably contributes in some cases. There are no useful diagnostic tests available to confirm sensitization.

Fluoroquinolones

This class of antibiotics is increasingly popular with the rise of drug-resistant bacteria and because many have an oral formulation that can be used for outpatients. As a class, they are very well-tolerated. GI-related side effects are the most common side effect; photosensitivity, QT_c prolongation, rash, liver-function enzyme abnormalities, and central nervous system effects have also been reported (30). Anaphylactic/anaphylactoid reactions have a reported incidence of 0.46–1.2/100,000 patients (29), and TEN has been documented in case reports (32).

True allergic reactions occur but are usually very rare. As with all the non-beta-lactam antibiotics, skin testing has not been fully studied, but has been attempted (33). A successful desensitization protocol has been published (34).

Antivirals

Allergies to antiviral medications are most likely rare, but are not well-documented. As with many other medications, GI-related side effects are common, 21% in one placebo controlled study of acyclovir (35). Adverse reactions to anti-retrovirals are exceedingly common, yet true hypersensitivity reactions are rare. Anaphylaxis has been reported to many antiviral medications, including acyclovir and zalcitabine (36,37). Desensitization protocols for acyclovir have been published (36,38).

Table 3
Rapid Vancomycin Desensitization Protocol*

Time (h:min)	Concentration (mg/mL)	Fluid infusion rate (mL/min)	Vancomycin infusion rate (mg/min)	Cumulative dose (mg)
0:00	0.0001 ^a	1.0	0.00010	0
0:10	0.001	0.33	0.00033	0.0010
0:20	0.001 ^b	1.0	0.0010	0.0043
0:30	0.01	0.33	0.0033	0.0143
0:40	0.01	1.0	0.010	0.047
0:50	0.1	0.33	0.033	0.147
1:00	0.1	1.0	0.10	0.48
1:10	1.0	0.33	0.33	1.48
1:20	1.0	1.0	1.0	4.78
1:30	10.0	0.22	2.2	14.8
1:40	10.0	0.44	4.4	37

*Adapted from Wong (14).

^aTypical starting concentration in patients with severe systemic reactions to previous vancomycin infusions.

^bTypical starting concentration in patients with moderate reactions to previous vancomycin infusions.

Summary

With the exception of the sulfonamides, we have limited knowledge of drug metabolism, antigenic determinants, and other factors relevant to mechanisms explaining hypersensitivity reactions to the non-beta-lactam antibiotics. Additionally, diagnostic testing to confirm drug-specific immunologic responses to these agents is generally unavailable, except in certain situations when an intradermal skin test to a nonirritating concentration of the drug is used to confirm an IgE-mediated reaction suggested by the clinical history.

Despite the limitations in our ability to definitely establish the mechanism of a suspected hypersensitivity reaction, many patients who have had serious adverse reactions to sulfonamides or vancomycin may cautiously receive the drug using well-established challenge or desensitization protocols. Depending on the clinical situation and the expertise of the consulting physician, these drug-challenge principles may be appropriately used with other non-beta-lactam antibiotics in well-informed patients.

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