

CHAPTER 15

Drug allergy and *Hymenoptera* sensitivity

Allan T. Luskin, MD *Chicago, Ill.*

DRUG ALLERGY

Adverse reactions to drugs (ADRs) represent the majority of illnesses due to physician intervention. Surveys of hospitalized (medical) patients yield an ADR prevalence of 6% to 15%. ADRs are complicated by the frequent use of nonprescription drugs and by multiple drug prescribing. Allergic drug reactions probably account for only 6% to 10% of all ADRs. Allergy to drugs may affect 5% of the population; 15% categorize themselves as drug allergic.

ADR may be characterized as predictable (80%) or unpredictable. Predictable reactions include (1) overdose or toxicity, (2) side effect, (3) secondary or indirect effects, and (4) drug interactions. The most serious ADRs are toxic. Side effects represent the most frequent ADR and may be unavoidable at pharmacologic doses. Delayed side effects include carcinogenicity and teratogenicity. Secondary/indirect effects include consequences of the pharmacologic action of the drug that are not universal. Drug interactions are common due to frequent prescribing of multiple drugs.

Unpredictable ADRs include (1) intolerance (lowered threshold to normal pharmacologic actions), (2) idiosyncrasy (a qualitatively unusual, nonimmunologic reaction to normal pharmacologic doses in susceptible individuals; these may be genetically determined defects, such as hemolytic anemia associated with G6PD/primaquine), (3) pseudoallergic reactions (similar clinical manifestations and often similar pathogenic mechanisms to allergic reactions), and (4) allergic reactions (reaction between a drug and antibodies or sensitized T cells).

For a drug to be immunogenic, it must either be a complete antigen (insulin or foreign antiserum) or, more commonly, a hapten-protein complex. All usual immunologic mechanisms may be seen in ADRs. Drugs may produce pseudoallergic reactions that often use a nonimmunologic mechanism to activate common inflammatory pathways.

Specific diseases

Anaphylaxis is IgE mediated; anaphylactoid reactions require no previous sensitization and are not IgE

mediated. These are not rare and may be lethal. Penicillin anaphylaxis is not uncommon; a 1% mortality rate from anaphylaxis due to some chemotherapeutic agents is reported. Muscle relaxants and anesthetics may cause an IgE-mediated anaphylactic reaction. Approximately 10% of severe anaphylactic reactions are fatal.

Serum sickness reactions currently are most commonly seen with penicillin administration. Usual manifestations include skin eruptions, fever, joint symptoms, and lymphadenopathy.

Drug fever is a common ADR. Previous drug allergy and atopy is rare. Hectic fever pattern and shaking chills are common; relative bradycardia is not. Rashes, pruritus, and eosinophilia are helpful clues when present, but occur in a minority of instances. Associated organ dysfunction is common but mild. Mean lag time to fever is 21 days. Defervescence is rapid with drug cessation. Antimicrobial agents are the most common cause. Although distinguishing drug fever from other febrile diseases is difficult, most patients can be rechallenged with the offending agent without complications.

Drug-induced autoimmunity most commonly occurs with hydralazine, procainamide, and isoniazid, causing a systemic lupus erythematosus-like disorder. Antinuclear antibodies are invariably present, with antihistone antibodies the rule. Hypocomplementemia, ds/ssDNA, and circulating immune complexes are rare. Significant renal disease is not common. There appear to be hormonal, genetic (human leukocyte antigen), and metabolic predisposing factors.

Vasculitic syndromes, primarily leukocytoclastic vasculitis, may occur with the administration of any drug; penicillin and sulfonamides are the most commonly incriminated.

Virtually any drug may produce dermatologic manifestations. These are the most frequent manifestations of drug allergy. Almost any type of skin eruption may occur. Serious skin eruptions include exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The appearance of the rash is generally not helpful in determining the culprit drug. Exanthems may involve IgM or cell-mediated immunity (CMI). Contact dermatitis is typically associated with CMI.

From Rush Medical Center, Chicago, Ill.

Drugs can also induce pulmonary manifestations. Infiltrative diseases may be acute (as with nitrofurantoin) but are more commonly chronic, resulting in fibrosis. These generally are nonimmunologic and are associated with antineoplastic agents.

The most common drug-induced pulmonary manifestation is bronchospasm associated with aspirin (ASA). Adverse reactions to ASA occur most commonly in patients with chronic asthma and rhinosinusitis (35% prevalence). Many patients with positive ASA challenges have no positive history. Nonsteroidal antiinflammatory drugs (NSAIDs) frequently cross-react with ASA (20% to 100%), related to their ability to block the cyclooxygenase enzyme site in the arachidonic acid pathway. The classic response is asthma associated with nasooocular reactions, although pure nasooocular reactions may occur. Cross-reactivity with dyes and preservatives has been reported but has not been confirmed.

ASA desensitization appears to occur in all patients who are sensitive to this agent. Cross-desensitization with ASA and NSAIDs is a universal phenomenon. Desensitization persists for 2 to 5 days. Daily ASA administration maintains the desensitized state indefinitely. The mechanism for ASA sensitivity and desensitization is not clear. However, desensitization may allow the administration of NSAIDs in patients who require them.

Drug-induced hematologic reactions are common due to antigen-antibody reactions. Reactions involving lymphoid cells occur with phenytoin. Hepatic reactions may often be associated with fever, skin rash, and eosinophilia. Intrahepatic cholestasis (as with phenothiazines) resolves after drug withdrawal. More serious is hepatocellular damage (hydrazine, monamine oxidase inhibitors, hydantoins, and halothane). Mild renal manifestations may be seen in association with serum sickness and lupuslike reactions. Nephrotic syndrome may be associated with penicillamine and heavy metals. Drug-induced acute interstitial nephritis may account for 8% of all cases of acute renal failure. Penicillins and NSAIDs are most frequently implicated. The immunologic basis may be humoral or cellular in origin.

Diagnosis

The tests currently available for diagnosis of ADRs are generally not helpful, and temporal relationships are the most important diagnostic clue. Direct challenge may be performed when drug fever is the only manifestation. Skin testing for IgE sensitivity is reliable for complete antigens (chymopapain, streptokinase, xenogenic antiserum, and insulin). The low molecular weight haptens, with the exception of penicillin, are not generally amenable for skin testing.

CMI skin tests are generally not useful except in contact dermatitis. In vitro tests have not proved to be helpful, with the exception of IgG/IgM sensitization in hematologic reactions.

Management

The strategies for management revolve around prevention and avoidance by using less sensitizing agents, alternative drugs, screening patients before treatment when appropriate, and dosing by the oral route whenever possible. When patients are at increased risk, pretreatment protocols, such as with radiographic contrast media, may be extremely helpful. Induction of clinical tolerance with ASA and NSAIDs appears promising. Test dosing is most appropriate in patients with a history of sensitivity to local anesthetics. This involves cautious administration of the drug after initial skin prick testing.

Adverse reactions to local anesthetics generally are idiosyncratic (methemoglobinemia), are not related to a drug (psychomotor reactions or sympathetic stimulation associated with epinephrine), or toxic (central nervous system and cardiovascular effects). Allergic reactions (contact dermatitis, urticaria and angioedema, and anaphylaxis) are rare (1%).

Patients with negative skin prick test results at low concentrations can be given increasing doses of local anesthetic (xylocaine). False-positive intradermal test results with undiluted 1% solution of drug are common. No reactions to methylparaben or propylparaben were seen in one study, although it has been previously suggested they may cause ADRs.

Immunologic desensitization has been performed using standard treatment protocols with insulin and β -lactam antibiotics. After desensitization with β -lactam antibiotics, 30% of patients experience mild, transient allergic manifestations. Long-term penicillin desensitization has been maintained by the use of daily oral doses. When systemic allergies to insulin are noted, the insulin should not be discontinued. Rather, the next dose should be reduced to one third and increased slowly. Lapses in treatment require desensitization.

Sulfasalazine may cause a hypersensitivity reaction (2%) characterized by rash and fever. Slow oral "desensitization" has been described. This appears to be well tolerated but should not be performed if there is a history of severe reactions, such as Stevens-Johnson syndrome.

HYMENOPTERA SENSITIVITY

Guidelines for immunotherapy with venom (VIT) have been established. VIT prevents systemic reactions: 95% of patients receiving VIT have little or no clinical reactivity when subsequently stung. However,

a few patients are not completely protected, and some treatment failures have been reported. Protection can be maintained over many years. Evaluation of prolonged VIT reveals no significant sequelae. Even without VIT there is a normal natural history of loss of sensitization over time. Protective venom-specific IgG can be maintained with no significant toxicity. Systemic reactions on resting may develop, generally in patients who have low levels of venom-specific IgG, which can be increased by increasing the dose of venom. Adverse reactions to VIT occur at a rate and severity similar to other allergen immunotherapy.

Most fatal sting reactions occur in patients who have never had systemic reactions. Screening is not practical because of cost and because approximately 20% of the population may have positive skin test or RAST results. The other factors that better reflect the risk of anaphylaxis are not known. The anaphylactic risk for sensitized but previously nonreactive patients is less than 10%. Sensitivity appears to disappear over 2 to 3 years in 30% to 40% of patients. The frequency of systemic reactions in sensitized patients who have previously reacted may be as high as 60%. There is no test that will distinguish large local reactors from systemic reactors.

Sensitized patients whose previous reaction was large and local have a 5% to 10% risk of systemic reactions. Therapy generally has not been judged cost-effective. Adults and children with only cutaneous, non-life-threatening systemic reactions have different courses; these children do not have more serious reactions when restung. Of all systemic reactions, 60% in children are only cutaneous, compared with 15% in adults. The risk for a more severe reaction in adults is approximately 50% and they are therefore candidates for immunotherapy.

Individual sensitivity may vary. Approximately 25% of reactors will have positive skin test results at 0.01 $\mu\text{g/ml}$ but 25% will react only at 1 $\mu\text{g/ml}$. Sensitivity has been confirmed by RAST. The reactions at 1 $\mu\text{g/ml}$ appear to be specific and significant.

The duration of VIT is under study. Skin test reactivity will decrease in most, but not all, patients. Positive RAST results may persist despite negative skin test results. The clinical significance of this is uncertain. A decline in serum IgE to insignificant levels is associated with little risk of systemic reactions after VIT is discontinued; failures (4%) had received uneventful stings before their reaction, suggesting that allergy may be reacquired. Patients may need to be monitored closely after uneventful stings to determine whether resensitization has occurred.

The protective level of IgG in most patients is approximately 3 $\mu\text{g/ml}$. Above this level the systemic

reaction rate during the first 3 years is approximately 1.6%. A reaction rate of 16% is noted when the venom-specific IgE level is less than 3 $\mu\text{g/ml}$. Patients who have stopped VIT after 1 to 2 years appear to have a 25% systemic reaction rate, and they should be cautioned strongly not to discontinue VIT.

Cross-reactivity occurs among venoms; little cross-reactivity is noted between honeybees and vespids, but significant cross-reactivity exists within the vespids, predominantly yellow jacket and hornet, and to a lesser extent the polistes (wasps).

Fire ants are aggressive stingers, attacking man at a yearly rate of up to 13% of the exposed population. Sensitivity has been reported to be as high as 16%, with anaphylaxis in 0.6%. The fire ant typically delivers multiple stings that cause a small wheal, which is replaced in 18 to 24 hours by a tiny pustule. Exaggerated local reactions and anaphylaxis are reported. Fire ant venom contains biologically active alkaloids and protein components. Three low molecular weight polypeptides in the protein fraction are antigenic. Whole body extract contains these antigenic fractions. The commercial fire ant whole body extract can be a reliable skin test agent, but variability between manufacturers suggests that a panel of whole body extract preparations may give fewer false-negative results. Fire ant venom appears to identify approximately 40% of patients with large local reactions and all patients who appear at risk of anaphylaxis.

Drug allergy and *Hymenoptera* sensitivity

Which of the following statements is/are true with respect to local anesthetic sensitivity?

- Positive skin tests indicate the need to switch classes of local anesthetics for use in provocative dose challenges on a routine basis
- Paraben sensitivity accounts for most intolerant reactions to anesthetics
- Psychomotor reactions are the most common cause of adverse reactions to anesthetic agents
- The most frequent life-threatening complication associated with local anesthetics is an anaphylactoid reaction

Explanation: Positive skin test results with local anesthetic occurs both in patients with positive histories and in individuals who have no history of adverse reactions. Only rarely do these results represent immunologic sensitivity. Most patients can receive provocative dose challenge without intolerant reactions. Paraben sensitivity has been suggested but has not been confirmed in large

studies. Psychomotor reactions are the most common cause of ADRs with local anesthetics. However, the most common life-threatening complication is a toxic reaction.

Answer: c is true.

Which of the following statements is/are true with respect to ASA sensitivity?

- a. The incidence of ASA intolerance is 20% to 35% in patients with bronchial asthma
- b. ASA sensitivity may be accurately predicted by history and the presence of nasal polyps
- c. ASA causes an IgE-mediated nasoocular reaction without change in FEV₁ in approximately 30% of adverse reactions
- d. ASA may cross-react with ingested compounds such as BHA/BHT and tartrazine frequently enough to make dietary manipulation a wise choice in most patients with chronic asthma who have nasal polyps
- e. "Desensitization" by ASA will block adverse reactions to naproxen

Explanation: The incidence of ASA sensitivity is 20% to 35% in patients with chronic asthma and rhinosinusitis/nasal polyps, but 5% in patients with asthma in general. Thirty-five percent of patients historically sensitive to ASA will not evidence ASA-intolerant reactions during challenge. Half of patients with positive challenges will have a negative history. Reactions to aspirin and NSAIDs may be nasoocular without any changes in flow rates. ASA sensitivity represents an idiosyncratic reaction of unknown cause (non IgE mediated). "Cross-reactivity" with ingested compounds has not been documented sufficiently to make dietary manipulation a reasonable course of action in most patients. A large study has failed to document any cross-reactivity with tartrazine. "Cross-reactivity" between ASA and the NSAIDs occurs with both the ADRs and the ability to induce "tolerance" or "desensitization."

Answer: e is true.

Match the following drugs with whether they are usually associated with allergic or pseudoallergic reactions (PARs).

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|--------------------------------|--------------------------------|
| 1. Chymopapain | a. PAR |
| 2. Insulin | b. Allergic (complete antigen) |
| 3. Codeine | c. Allergic (hapten) |
| 4. Indomethacin | |
| 5. Radiographic contrast media | |

Explanation: PARs mimic allergic reactions and often will share a common final inflammatory or reactive pathway. However, there is no evidence that the PAR involves antibodies or cell-mediated sensitization. Most drug reactions involve a reactive metabolite forming a hapten with a macromolecule. However, some antigens have a large molecular weight and are capable of functioning as a complete antigen. These generally include xenogenic antiserum, enzymes, and hormones.

Answer: 1-b, 2-b, 3-a, 4-a, 5-a.

Which of the following statements is/are true with respect to maintenance immunotherapy with *Hymenoptera* venom?

- a. Venom-specific IgE is maintained at a high sensitization level as long as VIT is continued
- b. Intervals of up to 6 weeks will allow for maintenance of protective levels of venom-specific IgG
- c. The incidence of long-term side effects with VIT is approximately 5% to 10%
- d. A VIT maintenance dose of 100 µg/ml every 4 to 6 weeks is recommended in all patients
- e. VIT can safely be discontinued in 95% of patients if a maintenance dose is reached after 1 to 2 years

Explanation: Venom-specific IgE levels will fall in patients receiving VIT, although not as rapidly as in patients who do not receive this therapy. A dosage schedule of every 6 weeks will maintain venom-specific IgG levels in most patients. There are no long-term side effects attributable to VIT. VIT cannot safely be discontinued after 2 years because the reaction rate approaches 25% in these patients. The generally accepted maintenance dose of VIT is 100 µg/ml. However, approximately 5% of patients do not achieve satisfactory IgG responses at this level. Most of those patients will achieve venom-specific IgG levels above 3 µg/ml if the dose of VIT is increased by 50% to 100%.

Answer: b is true.

Which of the following statements is/are true with respect to *Hymenoptera* skin testing?

- a. No whole body extract is appropriate for stinging insect sensitivity diagnosis
- b. Concentrations of venom extracts ≥ 1 µg/ml are not valid for skin testing because of the large number of false-positive reactions
- c. Multiple positive skin test results with various species may reflect multiple sensitivity or im-

munologic cross-reactivity, but not clinical cross-reactivity

- d. Skin testing is indicated in patients with progressively severe large local reactions
- e. Skin testing is indicated as a screening technique for sensitization in beekeepers only

Explanation: Whole body extract of fire ants contains amounts of the allergenic polypeptides that allow for reasonable sensitivity in predicting patients with potential fire ant venom-induced anaphylaxis. Concentrations of venom extract above 3 $\mu\text{g}/\text{ml}$ are associated with increasing numbers of false-positive reactions. However, 25% of anaphylactically sensitive individuals will have a reaction at only 1 $\mu\text{g}/\text{ml}$. Results of skin tests with venom from several species may be positive after only one sting. This may reflect immunologic cross-reactivity that may be clinically significant. This cross-reactivity is greatest among vespids; cross-reactivity between honeybees and vespids is minimal. Skin testing is not indicated in patients with progressively severe large local reactions because their risk of systemic reaction is not known. Skin testing will reflect sensitivity in most beekeepers and is not a valuable screening technique.

Answer: None are true.

IgE Hymenoptera venom sensitization:

- a. Is associated with at least 50 deaths per year
- b. Decreases spontaneously in almost all sensitized children
- c. Is more common in children than in adults
- d. Is evidenced by RAST or skin tests in 15% to 20% of a general population
- e. Is found in 90% of recently stung individuals

Explanation: Venom sensitivity causes 40 to 50 documented deaths per year; the actual fatality rate is probably higher. At least 90% of all children will have a gradual decrease in their level of IgE sensitivity; after 2 years, at least 60% will have negative skin test results. Sensitivity in children is far more common than in adults, but most deaths occur in adults. The incidence of venom sensitivity is high, occurring in 15% to 20% of the population, but this sensitivity disappears in approximately one third of people over two to three years. Ninety percent of recently stung individuals have positive skin test results, indicating venom sensitivity.

Answer: All are correct.