

Understanding drug allergies

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At this time, the incidence of adverse drug reactions can only be estimated because the intensive monitoring and documenting that is required to make this determination does not exist at most hospitals and clinics. Despite these limitations, a meta-analysis of prospective studies has estimated the incidence of serious adverse drug reactions in hospitalized patients to be 6.7% and the incidence of fatal adverse drug reactions to be 0.32%. When evaluating and managing the condition of a patient who has experienced an adverse drug reaction, the physician first obtains an accurate history and performs a careful physical examination to determine whether the reaction was immunologic in nature. Drug reactions that are immunologically mediated (1) require a period of sensitization, (2) occur in a small proportion of the population, (3) are elicited at drug doses far below the therapeutic range, and (4) subside after drug discontinuation in most instances. All possible culprit drugs should be identified, with dosages and dates of administration and discontinuation, and the patient should be asked about any previous drug exposure history. Although immunodiagnostic tests for allergic drug reactions are limited, several tests do exist and may be useful in the identification of drug-specific antibodies, drug-specific T lymphocytes, or mediators from activated cells. If the reaction was not consistent with an IgE-mediated event and if it did not involve serious organ damage, cautious rechallenge may be considered. For those reactions that appear to be IgE-mediated and for which there is no reliable skin test reagent, drug desensitization may be performed by allergists who are trained in this procedure. (*J Allergy Clin Immunol* 2000;105:S637-44.)

Key words: Adverse drug reactions, allergic drug reactions, drug allergy, drug desensitization, haptens, hypersensitivity reactions, toxicity

More intensive monitoring and documentation are needed at most hospitals and clinics in the United States to accurately report the incidence of adverse drug reactions (ADRs), which is thought to be high. Allergic drug reactions represent a subset of ADRs and are important causes of morbidity and death. This article will review the estimated incidence of ADRs, the features and classification of allergic drug reactions, and the mechanisms of hypersensitivity reactions. Priorities in the evaluation and management of the conditions of patients who have experienced allergic drug reactions also will be discussed.

Abbreviation used

ADR: Adverse drug reaction

ESTIMATED INCIDENCE OF ADRs

Overall incidence and clinical significance

Although most studies of ADR incidence that are currently available in the literature have been performed in Europe, a number of US studies also exist. In 1998, Lazarou et al¹ performed a meta-analysis of 39 prospective studies from US hospitals and estimated the overall incidence of ADRs in hospitalized patients to be 6.7%, with a 0.32% incidence of fatal ADRs. When both serious and nonserious ADRs were considered together, the percentage more than doubled, to 15.1% of hospitalized patients. In 1994 alone, 2,216,000 hospitalized patients in the United States had serious ADRs, and more than 100,000 of these reactions were fatal. Lazarou et al¹ concluded that the incidence of serious and fatal ADRs that were experienced by hospitalized patients in the United States was extremely high, with fatal ADRs ranking between the fourth and sixth leading cause of death. Whereas most ADRs are nonallergic in nature, 6% to 10% may be attributed to an allergic or immunologic mechanism.²

Incidence of cutaneous ADRs

Typically, the most commonly encountered ADRs are cutaneous reactions. Two of the largest investigations of the incidence of cutaneous ADRs are the Boston Collaborative Drug Surveillance Program³ and a study by Hunziker et al.⁴ Using a case-control study design, the Boston group evaluated more than 37,000 patients and found that cutaneous adverse reactions occurred in about 2% of hospitalized patients. The drugs most commonly observed as the cause of these reactions were ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole.³ Hunziker et al⁴ reported a similar though slightly higher incidence (2.7%) of cutaneous adverse reactions in hospitalized patients. This finding was based on a 20-year period of monitoring for adverse skin reactions at 3 hospitals. The most commonly involved drugs were similar to those reported in the Boston study and included penicillin and sulfamethoxazole.⁴

CHARACTERISTICS OF ALLERGIC DRUG REACTIONS

Definition of terms

To clearly understand the terms used to describe allergic drug reactions, it is important to recognize how they

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FIG 1. Schematic shows direct haptenation by a drug (D) molecule, such as penicillin. The molecule covalently binds to proteins found in the serum or on the cell-surface membrane. (Adapted from Sullivan TJ. Drug allergy. In: Middleton EJ, Reed CE, Ellis EF, et al, editors. *Allergy: principles and practice*. St. Louis (MO): Mosby-Year Book; 1993. With permission.)

TABLE I. Features of allergic drug reactions

- Initial therapeutic course is uneventful.
- With no previous exposure, allergic reaction appears after several treatment days.
- Allergic reactions are restricted to a limited number of syndromes.
- The allergic reaction occurs in a small proportion of the population.
- The allergic reaction will occur at a dose far below the therapeutic range.
- Blood/tissue eosinophilia supports the involvement of an allergic process.
- The allergic reaction usually subsides after discontinuation of the drug.

are grouped under the much larger “umbrella” category of ADRs. ADRs are divided into predictable and unpredictable reactions. Predictable reactions are dose dependent, are usually related to the known pharmacologic actions of the drug, and are observed to occur in otherwise normal patients. Examples of predictable reactions include toxicity, side effects, secondary drug effects, and drug interactions.

In contrast, unpredictable reactions are dose independent, are often not related to the pharmacologic actions of the drug, and occur in susceptible patients. Some examples of unpredictable reactions include idiosyncratic reactions, allergic reactions, and pseudoallergic reactions. Clinically, pseudoallergic reactions resemble allergic reactions but are distinguished by the fact that an immunologic mechanism is not involved. From this point on, this review will focus on the characteristics of true allergic or immunologic drug reactions.

Characteristics of allergic drug reactions

Several clinical aspects are typically observed in patients who experience allergic drug reactions (Table I). First, the initial therapeutic course with the drug is generally uneventful because a period of initial sensitization is required. Therefore, if the patient who is allergic to a drug has had no previous exposure, the allergic reaction appears only after several treatment days. Second, true

allergic reactions are restricted to a limited number of syndromes that are generally accepted as allergic in nature, such as anaphylaxis, urticaria, contact sensitivity, and various cutaneous eruptions,⁵ among others. Additionally, the allergic reaction generally occurs in a small proportion of the population.

Another feature of allergic reactions that is important for the physician to remember is the tendency of patients to react at drug doses far below the therapeutic range. For this reason, the administration of a “test dose” of a drug to a patient who is potentially allergic may have serious clinical consequences. If the reaction is an IgE-mediated event and the patient has drug-specific antibodies from a previous exposure, even a small dose may trigger sufficient mast-cell mediator release to cause a very severe or even fatal anaphylactic reaction.

The presence of blood or tissue eosinophilia supports the presence of an allergic process in a patient who has experienced a reaction. However, the absence of eosinophilia does not ensure that an allergic process is not operative and should not be interpreted as evidence of the absence of allergy.

Still another feature of allergic reactions is that the reaction usually subsides soon after the discontinuation of the drug. However, exceptions may occur in some instances, because of the formation of drug metabolites that haptenate or covalently link to cell-surface proteins. The resultant immune reaction then continues beyond drug discontinuation, because the immunogen is still present. This may be the mechanism that occurs in certain sulfonamide allergic reactions.^{6,7} In addition, Kearns et al⁸ have shown that cefaclor metabolites may act in a similar manner.

Allergic drug reaction classification systems

Allergic drug reactions demonstrate characteristics that are common to immunologic reactions in general. In light of this, they can be organized under the Gell and Coombs classification system for immunologic reactions.⁹ This classification scheme has 4 categories: immediate hypersensitivity reactions (type I), cytotoxic antibody reactions (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions (type IV). Immediate hypersensitivity reactions are mediated by drug-specific IgE antibodies, whereas cytotoxic antibody reactions and immune complex reactions are mediated by drug-specific IgG and/or IgM antibodies. Drug-specific T lymphocytes are responsible for delayed-type hypersensitivity reactions. Unfortunately, allergic drug reactions are often difficult to classify according to the Gell and Coombs system, because the exact mechanisms responsible for many reactions are not known.

Clinical classification of allergic drug reactions

When evaluating a patient who has had an allergic drug reaction, the physician may find it useful to classify the reaction according to a clinical classification scheme (Table II).¹⁰ The reaction will either be systemic or organ specific. Examples of major systemic allergic reactions

include anaphylaxis, vasculitis, serum sickness, and drug fever. However, even for 1 reaction type, 1 or another mechanism may be operative. In the case of penicillin-induced anaphylaxis, drug-specific IgE antibodies are responsible for systemic mast-cell mediator release. In contrast, for dextran-induced systemic reactions, the reaction results from nonspecific mast-cell mediator release. IgE antibodies are not involved. Immune complex reactions are mediated by a mechanism that involves drug-specific antibodies, whereas for drug fever, the pathogenic mechanism is unknown.

Organ-specific drug reactions may involve any body organ, but they most commonly affect the skin (most likely because the skin is both metabolically and immunologically active). The types of drug-induced cutaneous reactions are numerous and include, for example, maculopapular eruptions, purpura, pityriasis rosea-like eruptions, erythroderma, exfoliative dermatitis, and urticaria/angioedema. Besides these reactions, hematologic, pulmonary, hepatic, renal, and other types of organ-specific drug reactions may be observed. The exact mechanism for the demonstrated reaction is often obscure and may, in fact, be multifactorial.

In some instances, the classification of a systemic or an organ-specific allergic drug reaction is straightforward (eg, when a patient experiences severe anaphylaxis because of penicillin or latex allergy). More often, however, classification is difficult because the mechanism that underlies the reaction is usually not known. Hypersensitivity reactions are typically uncommon and unpredictable and cannot be reproduced in animal models, which makes it particularly difficult to study their mechanisms for research or clinical purposes.

Drug hypersensitivity: the hapten hypothesis

Because drugs that trigger allergic reactions are often univalent chemical compounds of relatively low molecular weight, the question arises how these small compounds could initiate or trigger an immune response. Most drugs that cause hypersensitivity reactions must first be bioactivated, a process that occurs as the drug is metabolized. Generally, drug metabolism is regarded as a type of detoxification process, whereby drugs are converted from lipid-soluble, nonpolar compounds to more polar, hydrophilic compounds that are easily excreted. If a metabolite is not adequately detoxified, however, it may cause direct toxicity to cells or immune-mediated hypersensitivity.

Drug metabolism typically occurs as 2 different steps, phase I and phase II reactions. Phase I reactions are oxidation-reduction or hydrolysis reactions, and phase II reactions are conjugation reactions that result in the formation of inactive compounds that are easily excreted. Most often, a reactive metabolite formed by phase I metabolism is promptly detoxified and eliminated. However, reactive drug metabolites that are not detoxified may bind to proteins or nucleic acids, causing cellular necrosis or the production of an altered gene product, respectively, as part of a directly toxic effect. Reactive

TABLE II. Clinical classification of allergic drug reactions

Table available in print only.

Adapted from Sullivan TJ. Drug allergy. In: Middleton EJ, Reed CE, Ellis EF, et al, editors. *Allergy: principles and practice*. St Louis (MO): Mosby-Year Book; 1993. p. 1726-46. With permission.

metabolites of sulfonamides have been shown to act in this manner.^{11,12} Alternatively, reactive metabolites may act as haptens that bind covalently with cellular macromolecules such as serum proteins^{6,7} or cell-surface membranes.¹³ Such binding results in the formation of large, multivalent immunogens that may initiate an immune response. It is thought that hypersensitivity reactions to antibiotics may occur by way of this mechanism.

The work from our group has demonstrated that reactive sulfonamide intermediates may haptenate serum proteins, thus providing an explanation as to how sulfonamides may trigger immunologic reactions.^{6,7} These reactive metabolites normally are reduced by glutathione and then excreted, but, under certain circumstances, they may exceed the body's capacity for glutathione conjugation. The presence of haptenated proteins may be detected in the serum during the course of sulfonamide therapy, and these may be responsible for initiating hypersensitivity reactions, at least in some patients.^{6,7}

Penicillin is an example of a drug that may haptenate proteins directly, without previous metabolism (Fig 1). Alternatively, sulfonamides haptenate proteins indirectly, by forming reactive intermediates, after drug metabolism, that covalently bind to serum or membrane proteins (Fig 2). In the case of penicillin, the drug is degraded to its reactive forms, and enzymatic breakdown is not required. However, most drugs are not like penicillin in their ability to directly haptenate proteins and are more like sulfonamides, in that they must be metabolized before reactive derivatives can cause protein binding.

In the case of sulfonamides, our group has shown that a single 40-kd protein in the serum is haptenated.^{6,7} We speculate that perhaps a highly reactive intermediate is formed during hepatic metabolism. This intermediate, instead of reacting with a large number of proteins, haptenates only a few proteins because of its highly reactive state. The intermediate may actually bind to the enzyme responsible for its metabolism, but this has not been proved. Halothane too appears to act similarly.^{14,15}

Figure available in print only.

FIG 2. Schematic shows indirect haptentation by a drug (D), which must first be metabolized before haptentation can occur. Reactive metabolites bind covalently to serum proteins or to cell-surface proteins. *Drug is metabolized. (Adapted from Sullivan TJ. Drug allergy. In: Middleton EJ, Reed CE, Ellis EF, et al, editors. Allergy: principles and practice. St Louis (MO): Mosby-Year Book; 1993. With permission.)

EVALUATION OF THE PATIENT WHO IS ALLERGIC TO A DRUG

Initial evaluation

When evaluating and managing the condition of a patient who has experienced an ADR, the physician must first obtain an accurate medical history and perform a careful physical examination. The determination must be made regardless of whether the reaction was immunologic in nature. Obtaining an accurate medical history is a critically important step in making this determination. All possible culprit drugs should be identified and recorded, along with their dates of administration and discontinuation. It is also important to document drug dosage, especially if the reaction was due to a toxic rather than an immunologic event. The patient should be asked about any previous drug exposure history, and the determination should be made whether there is underlying hepatic or renal disease that may cause alteration in drug metabolism or excretion, respectively.

The physical examination may yield important information, particularly if the patient is still experiencing the drug reaction. Because the skin is often involved in drug reactions, the physician should examine it carefully. Even after a skin reaction has subsided, the patient may be able to volunteer useful information about the type of cutaneous eruption that occurred. In addition to the skin examination, a complete physical assessment is important to the determination of the extent of other organ involvement, if any.⁵

Once the physician identifies the suspect drug or drugs thought to be responsible for a particular reaction, the propensity for each of these drugs to cause the reaction demonstrated should be determined. The *Physicians' Desk Reference*¹⁶ may be consulted for this purpose. Another reference, the *Drug Eruption Reference Manual*,¹⁷ is useful for evaluating the types of adverse reactions that are associated with particular drugs. This manual lists more than 370 commonly prescribed over-the-counter

drugs and the various adverse reactions each drug may cause (especially cutaneous reactions).

Clinical approach

Clinically, the diagnosis of a patient's illness as a reaction that was induced by a specific drug (and not a medical problem caused by something else) is often challenging. The easiest approach is the "better safe than sorry" tactic,¹⁸ in which the physician assumes that the reaction was drug related. The physician then informs the patient about the sensitivity to a particular drug and advises the patient not to accept therapy with the drug again. This approach is one of the safest ways to protect the patient against further drug reactions, but it is associated with several problems. First, the patient may be needlessly deprived of important therapeutic drugs, including those in the same therapeutic class, which limits future options if that drug therapy is again required; and second, the patient may be erroneously labeled as having multiple drug allergies.

In general, physicians prefer the "better safe than sorry" strategy over other possible clinical approaches. At our institution, we have noted that the frequency with which physicians order penicillin skin tests has declined. To confirm this observation and to obtain a better understanding of clinical decision making with respect to suspected drug allergy (specifically, suspected penicillin allergy), we performed a survey.¹⁹ A total of 601 surveys were distributed to general medicine and surgery physicians; 93 surveys were returned, for a response rate of 16%. Physicians who responded to the survey were presented with hypothetical clinical encounters in which penicillin was the drug of choice for patients with mild, moderate, or life-threatening infections. The patients were described as having either a vague history of penicillin allergy or a convincing history of penicillin allergy consistent with an IgE-mediated process. The survey respondents were asked to choose the type of antibiotic treatment for these patients.

When presented with patients who had a vague history of penicillin allergy, most physicians (52%) chose cephalosporin therapy for patients with mild, moderate, or life-threatening disease. For patients with a convincing history of penicillin allergy, most physicians selected erythromycin for mild disease (53%), quinolones for moderate disease (42%), and vancomycin for life-threatening disease (61%). Only one physician requested penicillin skin testing to determine whether the patients were currently allergic (ie, had penicillin-specific IgE antibodies), and only two physicians indicated that they would consult an allergist to perform penicillin desensitization.¹⁹

Skin testing of patients with suspected penicillin allergy, when reagents are available, is an important clinical option to consider, rather than turning immediately to broad-spectrum antibiotics, because of the increasing prevalence of antibiotic resistance. In our institution, in particular, we have encountered vancomycin-resistant enterococcus as a problem of increasing severity. In addition, patients with a history of peni-

cillin allergy often are found to have negative penicillin skin tests and can thus receive the antibiotic safely. Based on the results of our survey, we concluded that relatively few physicians at our institution are fully aware of their clinical options when confronted with a patient reporting a history of penicillin allergy. We now are working with the pharmacy department to improve physician education in this area.

In addition to the "better safe than sorry" tactic, other clinical approaches are available. First, on the basis of the results of a thorough history and physical examination and along with the knowledge of the pharmacologic properties of the drug, the physician should analyze the adverse reaction to determine whether it was in fact drug induced and, if so, whether it was a predictable reaction that is common and related to the pharmacologic properties of the drug or an unpredictable reaction that is rare and typically not related to the drug's pharmacologic properties. Predictable reactions include toxicity, side effects, secondary effects, and drug-drug interactions, whereas drug intolerance, idiosyncrasy, and allergy all fall into the unpredictable category.

For predictable reactions such as toxicity, a dosage adjustment may be all that is required. For other predictable reactions, the severity of the reaction must be assessed before a determination can be made about whether the drug can be readministered because, in most instances, the reaction will recur. For reactions caused by drug-drug interactions, an agent may be readministered as long as no additional drugs are given that may potentiate its actions.

In the unpredictable category, reactions may be mild or severe. Tinnitus with aspirin administration is an example of a drug intolerance and, in most cases, is a mild reaction. On the other hand, skin necrosis with the administration of warfarin (Coumadin) in patients with protein-C deficiency is a life-threatening idiosyncratic reaction, and, for this reason, the drug should not be readministered. Immunologically mediated drug reactions too may or may not be severe. Therefore, before a drug that caused a presumed immunologic reaction is readministered, it is best to determine the type of allergic reaction that was elicited and to determine the status of the allergic state (ie, whether the patient is currently allergic) at the time of evaluation.

Diagnostic tests for drug hypersensitivity

Although diagnostic testing methods exist, overall they are still of limited practical value for the clinician who is evaluating a patient with a suspected drug allergy. One major problem that affects the use of diagnostic tests for drug allergy is that, in most cases, except for penicillin, the immunochemistry of the drug in question still is not known.²⁰

Skin testing

In vivo skin testing for immediate hypersensitivity is available for compounds of high molecular weight and for penicillin but unfortunately not for other antibiotics.

When used for high-molecular-weight compounds such as foreign antisera, hormones, enzymes, and toxoids, testing may be helpful in the clinical evaluation. These particular agents are immunogenic in their native form and are able to induce the formation of antibodies and to trigger the cross-linking of IgE on the surface of mast cells. In contrast, for low-molecular-weight drugs, the clinical value of skin testing is unclear, largely because the relevant immunogens have not been identified.

The immunochemistry of penicillin is well understood. Penicillin is degraded to a number of clinically relevant products, and if these products are used in penicillin skin testing, the predictive value of testing for drug-specific IgE antibodies is very high. However, it must be emphasized that this test evaluates IgE-mediated allergy only.

When evaluating patients for IgE-mediated drug allergy to antibiotics other than penicillin, an allergist may obtain useful information from skin testing with the native drug. However, in light of the fact that it is not clear whether appropriate antigenic determinants are being presented, a negative result must be interpreted with caution. In contrast, a positive result may be very informative. If a nonirritative concentration is used in the testing, a positive result suggests the presence of drug-specific IgE antibodies. This work currently is being extended by our group.^{21,22} It is important to realize that, whereas some intravenous formulations of some antibiotics may be used as test reagents in their undiluted forms, others (such as ciprofloxacin) are highly irritative and must be used at very dilute concentrations.

At our institution, drug allergy skin tests always are performed in duplicate. The results of intradermal skin testing help to predict the safe dosage for beginning desensitization. A positive skin test indicates that IgE antibodies to the drug are present. However, if the skin test is negative, the presence of drug-specific IgE antibodies cannot be ruled out. It is possible that these antibodies are, in fact, present but are not detected by the test because the relevant immunogen was not used as the skin test reagent. Nevertheless, if the test is negative and the drug is required, drug desensitization can be initiated, with the intradermal amount administered to the patient as the starting dose for the procedure.

Other diagnostic tests

In vitro testing methods may provide valuable information to researchers, but often they are of limited use to the practicing clinician. The RAST, which is used to detect IgE antibodies, is not very sensitive for the detection of drug-specific IgE antibodies. In addition, drug-specific IgG and IgM antibodies may be measured also, but the detection of these antibodies in a patient with suspected drug allergy must be interpreted in light of the clinical picture. The presence of penicillin-specific IgG antibodies in combination with unambiguous clinical signs, such as massive hemolysis, is clearly meaningful. However, in the absence of clinical signs or symptoms of allergy, the presence of drug-specific IgG or IgM anti-

bodies may be only an epiphenomenon, and they may not be clinically relevant.

Clinicians should be cautioned about *in vitro* diagnostic tests for drug allergy that are being advertised by laboratories that specialize in allergy and immunology. RAST and the UniCAP (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden) assays are used by some commercial laboratories to detect drug-specific IgE antibodies to select antibiotics. However, despite the fact that these laboratories state that these tests are available, their usefulness is unclear. The same problems that plague skin testing plague the *in vitro* assays as well. Lack of knowledge of the clinically relevant antigenic determinants makes interpreting a negative finding difficult. Whereas the laboratory report may state that no drug-specific IgE antibodies are detected, it is just as likely that the antibodies are present but are not detectable because the antigen, coupled to the test disc, is not the clinically relevant one. Until there is more information about the correct immunogenic determinants of the various antimicrobial agents, *in vitro* assays for IgE antibodies to these agents have limited, if any, use in the diagnostic evaluation of the patient with a drug allergy.

Assays to measure serum complement components in the patient with a drug reaction can be performed to detect and assess complement activation, but these typically are not often used in the clinical evaluation. The release of various inflammatory cell mediators in blood and serum during or after an allergic reaction also can be measured. For example, the release of histamine by mast cells and/or basophils can be evaluated. However, for the most part, these tests also are largely research tools, not routine methods used in the clinical assessment. One exception is the serum tryptase determination. Tryptase is a protease that is found in mast cells, and it is released on systemic mast cell activation. At our institution, this test is included as part of the evaluation of patients with severe drug reactions that appear to be mast-cell mediated. A positive result does not establish the presence of drug-specific IgE antibodies, but it is indicative of extensive mast-cell mediator release.

Lymphocyte blast transformation in response to a specific drug can be measured through diagnostic testing, although tests for blastogenesis currently do not have a role in clinical patient evaluation and management. Work by Nyfeler and Pichler²³ has shown that certain drugs, including sulfonamides, can induce the proliferation of drug-specific T lymphocytes, but the clinical significance of this is uncertain at this time. In the 1980s, the *in vitro* leukocyte cytotoxicity assay was developed to identify individuals who were susceptible to the toxic effects of reactive drug metabolites produced by paracetamol, aromatic anticonvulsants, and sulfonamides.²⁴ The assay system relies on the metabolic activation of these drugs to their reactive forms by phenobarbital-induced cytochrome P-450 enzymes. If peripheral blood mononuclear cells from individuals with certain genetic phenotypes are included in the incubation, cellular cytotoxicity results. Rieder et al^{11,12} have shown that sulfonamide

metabolites are directly cytotoxic to lymphocytes and that cytotoxicity is more frequently seen in individuals with a history of sulfonamide-induced hypersensitivity reactions. These susceptible individuals appear to have specific drug metabolism defects that enhance their responsiveness to the drug metabolites formed. This finding supports the hypothesis that there is a genetic predisposition to the development of hypersensitivity reactions to some drugs and that the leukocyte cytotoxicity assay may ultimately have a more important clinical role in patient assessment once we are able to determine a patient's drug-metabolizing phenotype.

Computer-assisted diagnosis and evaluation of ADRs (including the use of algorithms, statistical pattern matching, and artificial intelligence) is a growing area that holds promise for the future.^{20,25} However, at this time, this diagnostic approach needs further study and evaluation before it becomes a routinely useful clinical tool.

MANAGEMENT OF THE DRUG-ALLERGIC PATIENT

Drug desensitization: when should it be performed?

Desensitization is defined as the conversion of a patient with a drug allergy from a highly sensitive state to a state in which the drug is tolerated. The procedure is performed by the cautious administration of incremental doses of the drug to the patient over a period of hours to days. It is implemented in patients with known or presumed IgE antibodies to a particular drug for whom no alternative drug is available.

In the past, acute drug desensitization was considered an approach to the management of IgE sensitivity only. However, it is possible that modified forms of desensitization can be used to manage the condition of patients with drug-induced allergic reactions that are thought to be immunologic in nature but that are not IgE mediated. A more prolonged, slow type of desensitization has been reported to be successful in patients with drug allergy who have AIDS.²⁵ This procedure is performed over several days, during which the patient is continually exposed to small but increasing doses of the drug until a therapeutic dose is reached.

Procedure for desensitization

Acute desensitization (used for IgE-mediated allergy and lasting several hours) has been successful not only for patients with an allergy to penicillin but for those with allergic reactions to a variety of other drugs as well. With the procedure outlined by numerous researchers,^{10,26-30} successful desensitizations have been performed in patients who have had reactions to β -lactam antibiotics/cephalosporins, sulfonamides, vancomycin, pentamidine, clindamycin, and antituberculous agents.

Rapid desensitization should be performed in the hospital, typically on the hospital floor or in the intensive care unit with a crash cart available and nursing personnel

aware of the procedure taking place. In our institution, acute desensitization always is performed by an allergist. The drug required for therapy should be used for acute desensitization, and the starting dose can be determined from intradermal skin tests with the native drug. Typically, doses are doubled every 15 to 30 minutes; and vital signs, physical examination, and peak flow values are monitored regularly. Pretreatment with antihistamines and/or corticosteroids usually is not recommended.

One third or fewer patients may experience mild complications, such as pruritus or rash, and may need adjustments in the drug dose or dosing intervals and medications to relieve symptoms. In patients with severe complications, such as marked bronchospasm or hypotension, the desensitization procedure should be aborted.

Management of acute drug reactions

When managing the condition of a patient who is experiencing an acute allergic drug reaction, the physician should follow several general principles. First, if possible, the operative immunopathogenic mechanism should be identified. Second, the physician should attempt to identify the offending drug and then decide whether the drug should be withdrawn or continued. In some instances, there is little choice: the drug must be continued because there is no alternative therapy. Suppressive therapy may be introduced in that case. The risk, however, is that the reaction may continue to worsen and may progress to a severe disorder, such as Stevens-Johnson syndrome or toxic epidermal necrolysis. For this reason, patients who receive suppressive therapy should be monitored carefully and should be examined for possible mucous membrane involvement, ocular involvement, and progression of any skin eruption that may be present.

The multiple drug allergy syndrome

According to Sullivan,¹⁰ the multiple drug allergy syndrome is not simply a propensity to react in specific ways to specific classes of drugs; instead, it is the propensity to develop immune reactions to haptens and then to express a broad range of immunopathologic responses. It does appear that some individuals are more likely than others to develop drug-induced reactions. In fact, Sullivan et al³¹ found that patients who have one drug allergy are more likely to experience the development of an allergy to a second, unrelated agent when exposed to that agent. In 1989, Sullivan et al³¹ evaluated patients with penicillin allergy who were admitted to the hospital. Of 437 patients with penicillin allergy who were admitted, 312 patients were administered a non- β -lactam antibiotic for treatment purposes. Of those patients who were exposed, 21% experienced the development of an allergic reaction to this drug, which was totally unrelated chemically or immunologically to penicillin. These findings support the hypothesis that some individuals react more frequently to drug haptens and supports the existence of a multiple drug allergy syndrome. However, more recent work has not confirmed these findings,³² which indicates that further research is needed to determine whether, indeed, such a syndrome exists.

CONCLUSION

Information critical to the successful management of the patient with drug allergy includes accurate historic data, a carefully performed physical examination, and selected general and/or specific diagnostic tests. It is not unusual for an allergist to spend one hour or more gathering relevant medical history information. Questions about drug dosage, previous drug exposure, temporal relationship between drug administration and reaction onset, and clinical manifestations of the reaction should all be asked. If possible, alternative therapeutic agents should be selected for the patient.

Most important, it is imperative to determine whether drug therapy is necessary. If the culprit drugs tend to be antibiotics, the physician should implement measures to avoid infections. For patients with recurrent infections, the infection must first be documented with objective evidence, and then an underlying cause for the recurrence should be sought. For example, patients with recurrent sinusitis should be evaluated for underlying allergic rhinitis, immunoglobulin immunodeficiency, and possible structural abnormalities that may predispose to the development of infections.

Each drug can elicit a spectrum of ADRs. For that reason, before implementing drug therapy, the physician must first weigh the risks and the benefits of that therapy. Only with better physician and patient education and the implementation of more judicious prescribing practices will drug-associated morbidity begin to decline.

REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
2. DeShazo R, Kemp S. Allergic reactions to drugs and biologic agents. *JAMA* 1997;278:1895-906.
3. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 152,438 consecutive inpatients, 1975 to 1982. *JAMA* 1986;256:3358-63.
4. Hunziker T, Kunzi U, Braunschweig S, Zehnder D, Hoigne R. Comprehensive hospital drug monitoring: adverse drug reactions: a 20-year survey. *Allergy* 1997;52:388-93.
5. Bernstein IL, Gruchalla RS, Lee RE, Nicklas RA, Dykewicz MS, eds. Disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol* 1999;83:December, Part 3.
6. Meekins CV, Sullivan TJ, Gruchalla RS. Immunochemical analysis of sulfonamide drug allergy: identification of sulfamethoxazole-substituted serum proteins. *J Allergy Clin Immunol* 1994;94:1017-24.
7. Gruchalla RS, Pesenko RD, Do TT, Skiest DJ. Sulfonamide-induced reactions in desensitized patients with AIDS: the role of covalent protein haptenation by sulfamethoxazole. *J Allergy Clin Immunol* 1998;101:371-8.
8. Kearns G, Wheeler GJ, Childress SH, Letzig LG. Serum-sickness-like reactions to cefaclor: role of hepatic metabolism and individual susceptibility. *J Pediatr* 1994;125:805-11.
9. Coombs R, Gell PGH. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell P, Coombs RRA, Lachman PJ, editors. *Clinical aspects of immunology*. Oxford (UK): Blackwell Scientific Publications; 1975. p. 761-81.
10. Sullivan TJ. Drug allergy. In: Middleton EJ, Reed CE, Ellis EF, et al, editors. *Allergy: principles and practice*. St Louis (MO): Mosby-Year Book; 1993. p. 1726-46.

11. Rieder MJ, Krause R, Bird IA, Dekaban GA. Toxicity of sulfonamide-reactive metabolites in HIV-infected, HTLV-infected, and noninfected cells. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;8:134-40.
12. Rieder MJ, Uetrecht J, Shear NH, Spielberg SP. Synthesis and in vitro toxicity of hydroxylamine metabolites of sulfonamides. *J Pharmacol Exp Ther* 1988;244:724-8.
13. Park B, Coleman J, Kitteringham N. Drug disposition and drug hypersensitivity. *Biochem Pharmacol* 1987;36:581-90.
14. Kenna JG. The molecular basis of halothane-induced hepatitis. *Biochem Soc Trans* 1990;19:191-5.
15. Martin JL, Kenna JG, Martin BM, Thomassen D, Reed GF, Pohl LR. Halothane hepatitis patients have serum antibodies that react with protein disulfide isomerase. *Hepatology* 1993;18:858-63.
16. Physicians' Desk Reference. Montvale (NJ): Medical Economics; 1999. p. 1-3346.
17. Litt J, Pawlak WA Jr, editors. Drug eruption reference manual. Cleveland (OH): Wal-Zac Enterprises; 1995.
18. Shear NH. Diagnosing cutaneous adverse reactions to drugs [editorial]. *Arch Dermatol* 1990;126:94-7.
19. Solensky R, Earl H, Gruchalla R. Clinical approach to penicillin allergic patients: a survey [abstract]. *J Allergy Clin Immunol* 1999;103:S33.
20. Weiss ME, Adkinson NF Jr. Diagnostic testing for drug hypersensitivity. *Immunol Allergy Clin North Am* 1998;18:731-44.
21. Brandt M, Gruchalla RS, Sullivan T. Skin-testing and in vitro testing to detect IgE to antimicrobial drugs [abstract]. *J Allergy Clin Immunol* 1993;91:263.
22. Empedrad RB, Earl HS, Gruchalla RS. Determination of nonirritating skin test concentrations of commonly used antimicrobial drugs [abstract]. *J Allergy Clin Immunol* 2000;105:S272.
23. Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy* 1997;27:175-81.
24. Spielberg SP. In vitro assessment of pharmacogenetic susceptibility to toxic drug metabolites in humans. *Fed Proc* 1984;43:2303-13.
25. Naranjo CA, Shear NH, Lanctot KL. Advances in the diagnosis of adverse drug reactions. *J Clin Pharmacol* 1992;32:897-904.
26. Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in the HIV-infected patients. *J Allergy Clin Immunol* 1994;93:1001-5.
27. Sullivan TJ. Antigen-specific desensitization to prevent allergic reactions to drugs [editorial]. *Ann Allergy* 1994;73:375-7.
28. Anne S, Middleton E Jr, Reisman RE. Vancomycin anaphylaxis and successful desensitization. *Ann Allergy* 1994;73:402-4.
29. Gruchalla RS. Acute drug desensitization. *Clin Exp Allergy* 1998;28(suppl):63-4.
30. Knowles S, Shapiro L, Shear NH. Serious dermatologic reactions in children. *Curr Opin Pediatr* 1997;9:388-95.
31. Sullivan TJ, Ong RC, Gilliam LK. Studies of the multiple drug allergy syndrome [abstract]. *J Allergy Clin Immunol* 1989;83:270.
32. Khoury L, Warrington R. The multiple drug allergy syndrome: a matched-control retrospective study in patients allergic to penicillin. *J Allergy Clin Immunol* 1996;98:462-4.