The Truth About Drug Allergies

Drug allergies are common and can be best understood and diagnosed by thinking in terms of the immune mechanisms involved in the reactions they cause.

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Serious adverse drug reactions are common. They account for 6.7% to 12.3% of hospital admissions, while drug allergies account for 10% to 25% of these reactions.[1,2] There are three significant consequences of allergic drug reactions:

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- The morbidity or mortality of the reaction itself;
- The necessary avoidance of the drug or related drugs in the future; and
- The necessary use of potentially less effective, more expensive or more toxic drugs in the future.

It appears, however, a history of drug allergy is far more common than the actual presence of drug allergy.[3,4]

Current Drug Allergy

To compare historical drug allergy with current drug allergy, it is necessary to have some means of detecting the latter condition. When examining the presence of true drug allergy in penicillin allergy, less than 10% of patients with a history of

penicillin allergy are actually found to be allergic to penicillin on skin testing.[3] In addition, in patients with proven immediate allergy to penicillin, less than 10% retain their allergy after a period of 10 years.[5] Current penicillin allergy is, therefore, much less frequent than a history of penicillin allergy. There is no reason to believe the situation is different for patients allergic to other medications, where diagnostic reagents are not available. This means a large proportion of individuals suspected of being allergic to one or more drugs potentially would tolerate the drug(s) if they were administered. In most circumstances, the only way to determine a true allergy is by challenging, although there are some exceptions to this statement, which will be discussed below.

Most drugs are low-molecular-weight molecules that are not immunogenic themselves. To stimulate an immune response, it is necessary for the compounds to bind or chemically interact with a large macromolecule — almost always a protein — forming a hapten carrier complex. It is this complex that forms the immunogen.

The generation of immunogenic hapten determinants can occur in several ways. The drug may bind to a soluble protein, which is then taken up by an antigen-processing cell. This generates immunogenic peptides that are re-expressed in association with the major histocompatibility complex (MHC) Class II molecules and presented to specific helper T cells. Another way the generation of immunogenic hapten determinants can occur is if the drug interacts with an intracellular protein and is presented in association with MHC Class I to cytotoxic T cells. Finally, drug interactions with

Summary

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- Current penicillin allergy is much less frequent than a history of penicillin allergy. There is no reason to believe the situation is different for allergy to other medications.
- It is unusual to develop an allergy to a drug that has been taken regularly for several months or years, unless there have been variations in compliance.
- The approach to a current drug reaction is similar to a historical drug allergy. The information gleaned from the clinical presentation is readily apparent and the drug history is most important.
- There are certain danger signs in allergic drug reactions that require careful consideration and, in most situations, preclude the re-administration of the implicated drug as a simple challenge. Such danger signs include:
  - — The presence of anaphylaxis or urticaria and angioedema;
  - — Rash with mucosal involvement or significant desquamation or exfoliation;
  - — The presence of drug fever or major organ involvement; and
  - — The presence of vasculitis, or a history of anemia, leukopenia or thrombocytopenia induced by the drug.
- Often, the diagnostic criterion used for diagnosing drug allergy is the response to re-challenge. Before carrying out a challenge in a potentially drug-allergic individual, it must be determined if it is truly necessary to re-administer the drug.

In patients with proven immediate allergy to penicillin, less than 10% have retained their allergy after a period of 10 years.

MHC Class I or Class II itself may occur, rendering these molecules and the peptides they contain foreign to the host T cells.[6,7] These mechanisms may then generate immune responses, based upon the Gell & Coombs classification as Type I or immunoglobulin E (IgE) antibody-mediated via mast cell degranulation. Such responses may precipitate immediate or anaphylactic sensitivity, which may be characterized by the following:

- Type II or cytotoxic, mediated by immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies;
- Type III or immune complex-mediated, caused by complexes of the drug-carrier molecule with IgG antibodies; and
- Type IV or cell-mediated immune reactions, which may be contact in type or by an immune response directed at specific organs, such as the lung, kidney or liver.

Some drug reactions thought to be allergic cannot be conclusively shown to fit into this classification. This is a reflection of our lack of knowledge of the antigenic determinants of most drugs and the lack of funding for clinical studies.

The kinetics of drug allergy are similar to those of immune responses. The onset of a reaction in one to three days after starting the drug means the patient is probably presensitized or that the hapten-carrier complex involves MHC molecules. *De novo* immune sensitization usually requires a minimum of eight to 10 days, and many drug allergies will develop within the first two to three weeks of therapy. It is unusual to develop an allergy to a drug that has been taken regularly for several months or years, unless there have been variations in compliance.

Clinical Approach

The clinical approach to a patient with a previous history of drug allergy involves obtaining a detailed history, by asking the following:

- How long ago did the reaction occur and is there any documentation regarding the nature of the reaction?
- How long after starting the medication did the reaction develop?
- What was the nature of the reaction (*i.e.,* Was there a rash and, if so, what type? Was there mucous membrane involvement? Did the rash come and go? Was there fever? Did the reaction resolve with discontinuation of the medication?)

- Were any other medications taken at the time of the reaction? Have these been taken again since?
- Have there been subsequent exposures to the same or similar medications? If so, persisting allergy to the implicated drug is unlikely.

The approach to a current drug reaction is similar. The information gleaned from the clinical presentation is readily apparent and the drug history is most important. Many patients currently take multiple medications, so a complete drug history is necessary. The following questions, therefore, should come to mind:

- Remembering the kinetics of drug allergy, when were these medications started?
- Has there been any concurrent or preceding illness?
- While hives or other rashes are not infrequent in viral infections, is there any previous history of drug allergy?
- Which drugs are the most likely to precipitate an allergic response?

Using the information obtained, a physician should be able to identify the most likely cause of the reaction and determine what happens when that drug is discontinued. If correctly identified, the reaction should resolve, although this may take several days. Sometimes it is impossible to implicate a single drug using these criteria, and more than one drug may have to be stopped. If substitute therapy is needed, it should be with an unrelated medication.

Danger Signs

There are certain danger signs in allergic drug reactions that require careful consideration and, in most situations, preclude re-administering the implicated drug as a simple challenge. Such danger signs include:

- The presence of anaphylaxis or urticaria and angioedema;
- Rash with mucosal involvement or significant desquamation or exfoliation;
- The presence of drug fever or major organ involvement; and

The most common form of drug allergy is the delayed-onset morbilliform or maculopapular rash, which develops four to six days or more after starting a medication.

- The presence of vasculitis, or a history of anemia, leukopenia or thrombocytopenia induced by the drug.

In the case of immediate drug allergy, it may be possible to carry out a rapid desensitization protocol, which will allow a therapeutic course of the implicated drug to be completed. This is most well documented in the case of penicillin. The desensitized state is only temporary, is specific only for the implicated drug and is lost approximately two days after the medication is discontinued. For non-IgE-mediated reactions, especially maculopapular reactions, a slow, incremental increase in drug dosage may be carried out over several days. In most cases, it is uncertain whether this is a true desensitization or misdiagnosis of drug allergy, or a loss of drug sensitivity. Validated protocols exist for sulphonamides.[8]

The most common form of drug allergy is the delayed-onset morbilliform or maculopapular rash, which develops four to six days or more after starting a medication. The mechanism of this reaction is unknown in most cases, but may be associated with cell-mediated or IgM-mediated immunity.[9,10] This type of rash often does not occur on re-

challenge with the implicated medication and, in the case of penicillins, is frequently associated with concomitant viral infections.

Diagnostic Testing

There are few diagnostic tests available for drug allergy. Tests that are available are best validated for penicillins, where skin testing with the major and minor antigenic determinants of benzylpenicillin detect IgE-mediated allergy. Skin tests also can be carried out with semisynthetic penicillins and cephalosporins, whose reactions are often specific for side-chain determinants. The sensitivity and specificity of skin testing with these antibiotics, however, have not been adequately assessed.[10]

Allergy to a drug is not necessarily a life-time state and may disappear over time in the absence of re-administering the drug.

There are anecdotal reports of skin tests for immediate or delayed reaction to other medications — particularly other antibiotics, anesthetics and muscle relaxants. The sensitivity and specificity of these tests, however, are unknown. Delayed hypersensitivity to beta lactams appears to be detectable by patch or intradermal testing in some cases (probably less than 50%).[11] Blood tests are available only for the presence of IgE antibodies to the major penicilloyl determinant by radioallergosorbent testing (RAST). There is a risk of missing approximately 20% of penicillin-allergic individuals if this is the only test relied upon. There are experimental RAST assays for other drugs, but none are available commercially.[12]

Often, the diagnostic criterion used for diagnosing drug allergy is the response to re-challenge. Before carrying out a challenge in a potentially drug-allergic individual, it must be determined if it is truly necessary to re-administer the drug. This is most often the case when the medication is essential and there is no effective or suitable substitute. Sometimes challenge will be performed if the diagnosis of drug allergy is truly questionable or after negative skin testing with penicillins. Challenge should not be undertaken if the initial reaction is consistent with one or more of the dangerous forms of drug allergy described above. How the challenge will be performed also should be determined.

For example, will it be a progressive challenge/desensitization beginning with small incremental increases in dosage, or will a full-dose challenge be carried out? The time between challenges must be decided upon as well (will increases in dose be half-hourly, as in immediate drug allergy, or daily for suspected delayed morbilliform reactions)? It also must be decided if the drug will be continued after successful challenge (is the challenge to be diagnostic or therapeutic?). Such decisions are best made by an allergist/clinical immunologist.[13]

Because of the availability of diagnostic testing for beta lactam antibiotics, the question of cross-reactivity between beta lactams has generated considerable interest. If cross-reactivity occurs it is generally most common with the first-generation cephalosporins and rarely with second- or third-generation cephalosporins. This may be due to:

- Structural similarities between first-generation cephalosporins and penicillins;
- Side-chain similarities between these drugs; and

- Cross-contamination of early first-generation cephalosporins with penicillin derivatives.

Post-marketing surveys suggest the risk of allergic reactions in penicillin-allergic subjects is not significantly increased with the use of second- and third-generation cephalosporins. Unfortunately, diagnostic tests with cephalosporins are not standardized and there is a lack of knowledge of the haptenic determinants of these antibiotics.[14]

Conclusion

Drug allergies are common, but a history of drug allergies is perhaps 10 times more frequent than current drug allergies. Drug allergies can be best understood and diagnosed by thinking in terms of the immune mechanisms involved in these reactions. Allergy to a drug is not necessarily a lifetime state and may disappear over time in the absence of re-administering the drug. Unfortunately, there are few diagnostic tests for drug allergy, and there has been little, if any, progress in this aspect of clinical practice. Clinical history and presentation, therefore, remain the most important methods of diagnosis. CME

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