

DIAGNOSTIC TESTING FOR DRUG HYPERSENSITIVITY

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Adverse drug reactions are important and frequent complications of medication therapy. Estimates are that 5% to 15% of patients develop adverse reactions to medication during treatment.^{19, 32} As many as 30% of hospitalized patients experience at least one adverse drug reaction.^{10, 32} Approximately 3% of all acute care medical admissions and 0.3% of all hospital admissions are attributed to adverse medication reactions.¹⁹ Fatal drug reactions occur in 0.1% of medical in-patients and 0.01% of surgical in-patients.¹⁹ Drug sensitivity has been implicated in 4.3% of deaths and 5.6% of cerebral damage in cases of anesthetic mishaps reported in the United Kingdom.²⁵ The first step in properly diagnosing adverse drug reactions is to understand the different types that can occur.

There are certain adverse drug reactions that may occur in all individuals.²⁰ These reactions include overdoses, which are toxic reactions caused by excessive doses or impaired excretion or metabolism of a medication. Side effects are undesirable but are potentially unavoidable because of the pharmacologic action of the particular medication, such as tremors with use of beta agonists. Secondary effects are undesirable effects that are unrelated to the primary pharmacologic action of the medication, such as oral candidiasis secondary to the use of inhaled steroids. Drug interactions involve the interaction of two or more drugs causing toxicity that otherwise would not be present, such as that seen with the terfenadine-erythromycin interaction. Other adverse drug reactions occur only in susceptible patients in an unpredictable manner. These include drug intolerance, which is caused by a lower threshold to the normal pharmacologic action of a particular medication, such as tinnitus seen at low doses of salicylates in selected patients; idiosyncratic reactions, which usually result from a genetically determined metabolic or enzyme deficiency that is not expressed under normal situations, such as hemolytic anemia occurring in patients with glucose-6-phos-

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phate dehydrogenase deficiency after receiving an oxidant drug; drug allergies that by definition involve immunologic mechanisms such as IgE penicillin anaphylaxis; and pseudo-allergies, which are reactions that have similar clinical manifestations as allergic reactions but the mechanism has been proven not to involve effector immune cells (antibodies or sensitized T lymphocytes). Allergic drug reactions (involving immunologic mechanisms) account for approximately 5% to 10% of adverse drug reactions.⁵

Properly diagnosing an offending medication as a cause of an adverse drug reaction is often difficult. Multiple medications are sometimes in use at the same time, and the clinical symptoms of adverse drug reactions may overlap with symptoms of the underlying disease. A common example is a patient who develops an exanthem. It is often unclear if the cutaneous reaction is related to the antibiotic prescribed or to the underlying infectious process.

Our general lack of knowledge of the immunochemistry of drug metabolism and immunoreactive metabolites also greatly hampers our ability to accurately use diagnostic tests to evaluate allergic drug reactions. Except for penicillin and to a lesser degree anticonvulsant medications and sulfonamides, our understanding of the immunoreactive metabolites and immunochemistry of medications is quite limited. At times we employ tests for drug-specific immune responses, but we lack knowledge of the positive and negative predictive value of these as diagnostic tests. This lack of knowledge is understandable because there are only a few studies in which large numbers of patients with negative and positive diagnostic tests have been rechallenged with the suspected medication.

Despite these difficulties, it is worth attempting to diagnose immunologic drug reactions. It is important to define the causal agent to help guide the selection and use of future medications for a given patient and to properly manage the present adverse drug reaction. Labeling a patient inaccurately allergic to a medication may cause the future use of less effective or more toxic medications as substitutes for the preferred medication.

DETERMINING THE CAUSE OF ALLERGIC DRUG REACTIONS

Detailed History

Although not traditionally believed to be a diagnostic test, a detailed medical history is significant in accurately diagnosing allergic drug reactions; we consider it the most important diagnostic procedure for the purpose of this article. To diagnose an allergic drug reaction properly, meticulous history taking is often required. The detailed history should include all medications regularly and intermittently used by the patient, including doses, indications, when initiated, and duration of therapy. The detailed history of the clinical manifestations of the reaction, including associated symptoms, is extremely valuable. Ongoing medical problems and conditions also should be inquired about in detail. Equally important information includes prior exposure to the same or structurally related medications, the effect of drug discontinuation, the treatment for the reaction to date, and the patient's response to the treatment.^{45, 65} If any diagnostic tests or rechallenges have already been done, these tests or rechallenge results are important. Knowledge of the medical literature with particular reference to the medications' known propensity for causing reactions is paramount. The proximity of drug administration to the onset of acute reactions should be determined; agents that have been used for long, continuous periods before the onset of an

acute reaction are less likely to be implicated than are agents recently introduced or re-introduced. Patients with a history of prior allergic reactions appear to have an increased risk of subsequent adverse drug reactions. It is often useful to do a MEDLINE search for all medications being considered as culprits for allergic reactions. It may also be useful to contact the pharmaceutical's manufacturer including the medications in question because they may have unpublished information including postmarketing reports of adverse reactions to their particular products. In complicated scenarios it is often useful to prepare a flow diagram to see better the reaction in relationship to medications received and ongoing therapy and treatment. The following are diagnostic tests for drug hypersensitivity:

- Detailed history
- Skin testing for immediate hypersensitivity reactions
- Patch testing
- Provocative drug challenge
- Radioallergosorbent test
- Measurement of drug-specific IgG or IgM antibodies
- Assays to measure complement activation
- Release of histamine and other mediators by basophils
- Measurement of mediators
- Lymphocyte blast transformation
- Leukocyte toxicity assay
- Computer-assisted evaluation of adverse events using a bayesian approach.

Recent studies have shown that when charts are reviewed by either physicians or hospital pharmacists there are significant inaccuracies in hospitalized patients' records concerning histories of medication allergies.^{2, 52} These inaccuracies underscore the need for a personally obtained detailed and accurate history about medication reactions.

IN VIVO TESTS

Skin Testing For Immediate Hypersensitivity Reactions

Although standardized skin tests are commonly used by allergists in the diagnosis of aeroallergen and Hymenoptera allergy, the evaluation of drug allergy is hampered by the relative unavailability of relevant drug metabolites or appropriate multivalent testing reagents. Skin testing has an established role in the evaluation of IgE-mediated penicillin allergy⁷⁴ and is also useful in the evaluation of allergy to muscle relaxants,^{23, 44, 69} barbiturates,^{23, 24, 44} chymopapain,²⁸ streptokinase,²¹ insulin,^{28, 30} latex,^{29, 64} and other miscellaneous drugs and most biologicals. Specific protocols for skin testing have been published in detail.^{4, 47}

For safety, a scratch or puncture (epicutaneous) test should be performed before the more definitive intradermal test. When skin tests are performed with the drugs or reagents that have not been well validated previously, all positive skin test responses should be confirmed by skin testing three to five normal individuals as appropriate controls to rule out irritative, false-positive skin responses.³ If normal controls are skin test negative using the same concentration, then the positive skin test in the patient can be considered to be immunologically valid. Skin testing cannot be done in the presence of medication that will affect the skin test response (e.g., H₁ antihistamines, tricyclic antidepressants).

sants, and high-dose sympathomimetic agents).⁷¹ Appropriate positive (histamine) and negative (diluent) controls should be used.⁴ Immediate skin testing is a bioassay that detects the physiologic response to mediators released from cutaneous mast cells when drug-specific IgE antibodies bound to skin mast cells are cross-linked by the drug in question. Preferably, skin testing should be performed 4 to 6 weeks after a drug reaction. Skin tests for drug allergy are primarily used for the confirmation of adverse reactions mediated by type I hypersensitivity.³

Tests for drug-specific immune responses are hindered because we rarely know the drug's immunochemistry. Because most drugs are small molecular weight chemicals, they are haptenic and must first combine with larger carrier molecules to stimulate an immune response and, subsequently, an allergic reaction.⁵⁰

In the case of penicillins, immunochemistry has been very well studied, and we know that the β -lactam ring opens up under physiologic conditions to form a covalent amide linkage with epsilon amino groups of lysine residues in serum and possibly membrane-bound proteins.^{38, 51} The resulting antigenic configuration, known as the *penicilloyl determinant*, elicits the dominant immune response in patients receiving penicillin therapeutically. The penicilloyl group has been designated the *major determinant* because approximately 95% of the penicillin molecules that irreversibly combine with proteins form penicilloyl moieties.^{37, 51} This reaction occurs with the prototype benzylpenicillin and virtually all semi-synthetic penicillins. Multiple penicilloyl determinants have been synthetically coupled to a weakly immunogenic polylysine carrier molecule to form penicilloyl-polylysine (PPL). Coupling multiple penicilloyl moieties to the polylysine carrier molecule increases the sensitivity of detecting IgE antibodies to this antigenic determinant four- or fivefold.³ Penicillin also can be degraded by other metabolic paths to form additional antigenic determinants. These derivatives are formed in small quantities and stimulate a variable immune response and have been termed the *minor determinants*.³⁹

The PPL reagent is commercially available in the United States as Pre-Pen. Because the minor determinants are labile and cannot be synthesized readily in multivalent form, skin testing for minor determinant allergen is usually accomplished using a mixture of native benzylpenicillin, its alkaline hydrolysis product (benzylpenicilloate) and its acid hydrolysis product (benzylpenilloate), collectively called the *minor determinant mixture* (MDM). Currently, an MDM is not commercially available in the United States. If one uses benzylpenicillin diluted to a concentration of 10,000 units per mL [10^{-2} M] as the sole minor determinant reagent, approximately 5% to 10% of skin test-reactive patients will be missed⁷²; however, some of those missed may be at risk for serious, anaphylactic reactions.²⁷ Nevertheless, this alternative to MDM is reasonable for use in patients without impressive histories of anaphylactic reactions.⁷³

Unlike many diagnostic tests for drug allergies, both the positive and negative predictive values of skin tests using penicillin reagents have been studied. When therapeutic doses of penicillin are given to patients with histories of penicillin allergy, but with currently negative skin tests to PPL and MDM, IgE-mediated reactions occur very rarely and are almost always mild and self-limited. Approximately 1% of skin test-negative patients will experience accelerated urticarial reactions, and approximately 3% will have other mild cutaneous reactions (Fig. 1).^{26, 73} Patients with histories of penicillin allergy and negative skin tests may become resensitized after subsequent uneventful penicillin administration, and repeat skin testing before future penicillin administration may be prudent. In general, with increasing time from the allergic reaction to penicillin,

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Figure 1. Prevalence of positive and negative penicillin skin tests, and subsequent allergic reactions in patients treated with penicillin (based on studies using both PPL and MDM as skin test reagents). *One study found 65% positive. †Amoxicillin and ampicillin have higher rates of cutaneous reactions. (Adapted from Weiss ME, Adkinson Jr NF: Beta-lactam allergy. In Mandell LG, Douglas Jr RG, Bennett JE (eds): Principles and Practice of Infectious Disease, ed 3. New York, Churchill Livingstone, 1989, p 264; with permission.)

the prevalence of skin test positivity to penicillin determinants decreases, although for some patients penicillin-specific IgE antibodies persist indefinitely.^{17, 67}

Studies have suggested that skin testing with major and minor determinants of benzylpenicillin may not detect all individuals with ampicillin/amoxicillin-specific allergy.^{11, 63} Therefore, some have advocated performing additional skin tests with native ampicillin/amoxicillin (20 mg/mL) or an aminopenicillin MDM if available.¹¹ For reasons that are currently unclear, the diaminopenicillins (ampicillin and amoxicillin) induce nonurticarial rashes with greater frequency than other penicillins.^{55, 58}

A limited number of patients with positive skin tests have been treated with therapeutic doses of penicillin. The risk of an anaphylactic or accelerated allergic reaction ranges from 50% to 70% in such patients (see Fig. 1)⁷²; therefore, if skin tests are positive, equally effective, non-cross-reacting antibiotics should be substituted when available. If alternative drugs fail, inducing unacceptable side effects, or they are less effective, the administration of penicillin can be considered using a desensitization protocol.⁷²

With the increasing use of cephalosporins, the risk of cross-reactivity between cephalosporins and penicillins continues to be an important question. In the case of first generation cephalosporins, there appears to be an increased risk for adverse reactions to cephalosporins among patients with a history of penicillin allergy.^{6, 62} The exact incidence of clinically relevant cross-reactivity between penicillins and early cephalosporins is highly variable among patients, and although probably small, cannot be dismissed on statistical grounds alone because

life-threatening anaphylactic cross-reactivity has occurred. The newer, second and third generation cephalosporins appear to have much lower cross-reactivity with penicillins, but this could be in part caused by less prevalent clinical use because of recent availability.

In the case of most drugs other than penicillins, we have little or no information about the predominant specificity of the drug-specific immune responses. Without such information, a negative skin test with the native drug may not indicate a true lack of allergy. If the skin tests are positive at concentrations at which normal subjects are negative, the patient may be presumed to be at significant risk for an acute allergic reaction if the drug is readministered.³ Without information concerning the drug's immunochemistry, a negative skin test to the native drug may not truly indicate a lack of immunologic sensitization,³ as has been shown for sulfonamide allergy. If the medication needs to be readministered it would be prudent to do that under a physician's supervision.

Interest and research in allergic drug reactions during the perioperative period has greatly increased.⁷⁵ In patients with allergic reactions during surgery, studies have shown that skin testing with nonirritative concentrations of medications used during the induction phase of anesthesia may help in determining which medication caused the allergic reaction.^{23, 24, 44, 69, 70}

Patch Testing

Patch testing is a form of drug challenge applicable at times in diagnosing drug-induced contact dermatitis.^{12, 13, 77} Patch testing is performed by applying a nonirritating concentration of the agents in question to an absorbent pad, which is then attached to the skin under hypoallergenic occlusive tape. At 48 and 72 hours the sites are inspected; a positive reaction is characterized by pruritus, vesiculation, and erythema. Interpretation of patch tests should be done carefully and by personnel experienced in reading patch tests. To date, patch testing has been relegated to a minor role in diagnosing allergic contact reactions to medication.

Provocative Drug Challenge

The ultimate or gold standard of *in vivo* tests is the provocative drug challenge. At times, the drug challenge is the only diagnostic approach that can demonstrate adverse reaction potential with certainty. Provocative drug challenge obviously poses certain risks to the patient that should not be taken lightly. Patients often are reluctant to undergo provocative drug challenge when they are convinced that a medication has caused them adverse effects. Individuals who have had toxic epidermal necrolysis, Stevens-Johnson syndrome, and severe anaphylactic reactions should probably never undergo provocative drug challenge.^{16, 56}

If provocative drug challenge is undertaken, it should be done using incremental dose challenges. A decision to challenge a potentially sensitive patient involves careful assessment of the risks and benefits derived from the drug challenge. Provocative drug challenges have recently increased with the AIDS epidemic. Approximately 40% of patients with AIDS have had adverse reactions to trimethoprim-sulfamethoxazole, which is one of the most useful medications to both prevent and treat *Pneumocystis carinii* pneumonia.^{9, 14} Faced with the knowledge that trimethoprim-sulfamethoxazole is the agent of first choice for

this problem, and with the high incidence of adverse reactions in HIV-positive patients, clinicians have developed various desensitization protocols in which doses of trimethoprim-sulfamethoxazole are incrementally increased.^{1, 15, 22, 34, 53, 66} Using trimethoprim-sulfamethoxazole desensitization protocols, approximately 50% of patients with prior reactions tolerate trimethoprim-sulfamethoxazole therapy. This approach is not risk-free, and serious adverse reactions have occurred using desensitization protocols.⁶¹ The decision to undertake a drug challenge should only be conducted by experienced health care personnel under controlled circumstances.

IN VITRO TESTING

Radioallergosorbent Test

The radioallergosorbent test (RAST) is a solid-phase, radio-immuno assay (RIA) that was first developed in 1967. The RAST measures circulating allergen-specific IgE antibody. The RAST and RAST analogs are performed by linking the allergen (drug) in question to a solid phase (e.g., carbohydrate particle, paper disk, or the wall of polystyrene test tubes or plastic microtiter wells).^{3, 4, 18} The drug attached to the solid phase is incubated with the patient's serum, during which time specific antibody of all immunoglobulin isotypes is bound. After washing, a second incubation is done with a radiolabeled, highly specific anti-IgE antibody. Following washes, the bound radioactivity is directly related to the drug-specific IgE antibody content in the original patient's serum. When appropriately done, RAST correlates well with skin test end point titration, basophil histamine release, and provocation test results.⁴⁸ Results from the serum under study are compared with a positive reference serum and negative control serum. Application of the RAST for the diagnosis of a drug allergy caused by IgE antibody has again been limited because of incomplete knowledge of the conformation of drug or its metabolite that acts as antigen or hapten. A RAST has been developed to measure IgE antibody to the major penicilloyl determinant of penicillin,⁷⁶ insulin,^{28, 30} chymopapain,²⁸ muscle relaxants,⁷ thiopental,³¹ protamine,⁷⁴ latex,^{43, 64} and others. False-positive tests may occur because of high nonspecific binding, high total serum IgE levels, or poor technique. False-negative tests may occur because of interference of high levels of IgG-specific antibodies or an inability to maximize assay sensitivity. RAST offers the advantage of being able to measure IgE-specific antibodies when patients cannot be skin-tested. The use of RAST to diagnose penicillin allergy is limited by the fact that RASTs for penicillin minor determinants are not currently available. If a RAST assay has not been developed to maximize sensitivity, clinically false negatives may give a false sense of security.⁴

Measurement of Drug-Specific IgG or IgM antibodies

Medications may produce drug-specific IgG or IgM antibody responses, but these usually have no associated pathologic consequences. With the exception of some cases of drug-induced thrombocytopenia, hemolytic anemia, and agranulocytosis, there often is no correlation between the presence or titers of drug-specific IgG or IgM antibodies and pathologic allergic drug reactions. Recent evidence suggests that certain protamine reactions may be mediated through

protamine-specific IgG antibodies.⁷⁴ Drug-specific IgG and IgM antibodies can be measured using solid phase RIA or ELISA tests.¹⁸

Assays to Measure Complement Activation

Assays to assess complement activation include assays of serum complement components (i.e., C4, C3) or total hemolytic component [C_{H50}] and measurements of products of complement activation (e.g., C3a, C4a, C5a). These assays, if positive, implicate complement activation in specific reactions but generally do not distinguish drug allergies from other adverse reactions, nor pinpoint a specific drug as the culprit.^{70, 71}

Release of Histamine and Other Mediators by Basophils

Washed leukocytes containing basophils with IgE antibody on their cell surface will release histamine and other mediators when incubated with relevant antigens. In general, results correlate with those of direct immediate skin tests. Haptenic drug allergens are often weak stimulants; therefore, as a diagnostic test, leukocyte-histamine release has a low sensitivity. The assay is relatively laborious, requires whole blood drawn immediately before the test, and is limited in availability to research laboratories in general.^{41, 68}

Measurement of Mediators in Serum and Urine

During and for a short time after allergic reactions, blood can be analyzed for the release of various inflammatory cell mediators such as histamine, prostaglandin D₂ chemotactic factors, and serum tryptase. Urine also can be analyzed for metabolites of histamine or prostaglandin D₂. Plasma histamine and prostaglandin D₂ levels remain elevated for only brief periods of time, limiting their clinical utility. Bioassays to measure chemotactic factor activity are cumbersome to perform and suffer from large interassay variability. Assays to measure serum tryptase (a protease released specifically from mast cells) are more promising in the clinical assessment of mast cell-mediated allergic reactions (anaphylaxis) because serum tryptase remains elevated for hours rather than minutes after mast cell degranulation.⁵⁷ Positive tests are more interpretable than negative results because there are many false-negative tryptase results.

Lymphocyte Transformation Assays

Lymphocyte transformation tests measure blastogenesis of lymphocytes by measuring the uptake of the DNA precursor, tritiated thymidine, after a sample of the patient's peripheral blood lymphocytes is cultivated with nontoxic concentrations of the suspected drug. An enhanced proliferative response in the presence of the suspected drug is interpreted as a sign of a drug-specific T-cell sensitization. The clinical value of these tests is hindered by the complexity of the procedure, the delay in obtaining results, the significant interlaboratory variability, and poor reproducibility over time.⁴⁹ Considerable disagreement exists about the value of the procedure in the diagnosis of drug allergy.⁸ At present, these tests need further validation before they have defined clinical utility.

Leukocyte Toxicity Assay for Drug Hypersensitivity

It has been shown that reactive drug metabolites may have a causative role in some serum-sickness-like drug reactions in susceptible patients. In the leukocyte toxicity assay, the drug in question is incubated with hepatic microsomes, prepared from mice as a source of oxidative enzymes, primarily cytochrome P-450. Peripheral blood lymphocytes from the patient in question are incubated with the above drug-microsome mixture, and the percentage of dead lymphocyte cells is measured and used as an index of toxicity of the drug metabolites generated (Fig. 2).

This approach, first pioneered by Spielberg,⁶⁰ demonstrated that acetaminophen could be metabolized *in vitro* to a metabolite that under appropriate conditions was toxic to human peripheral blood mononuclear cells.⁵³ These observations were subsequently applied to understand further the problem of severe hypersensitivity reactions to sulfonamides^{53, 54, 60} and aromatic anticonvulsants, such as phenytoin, phenobarbital, and carbamazepine.⁵⁹ These hypersen-

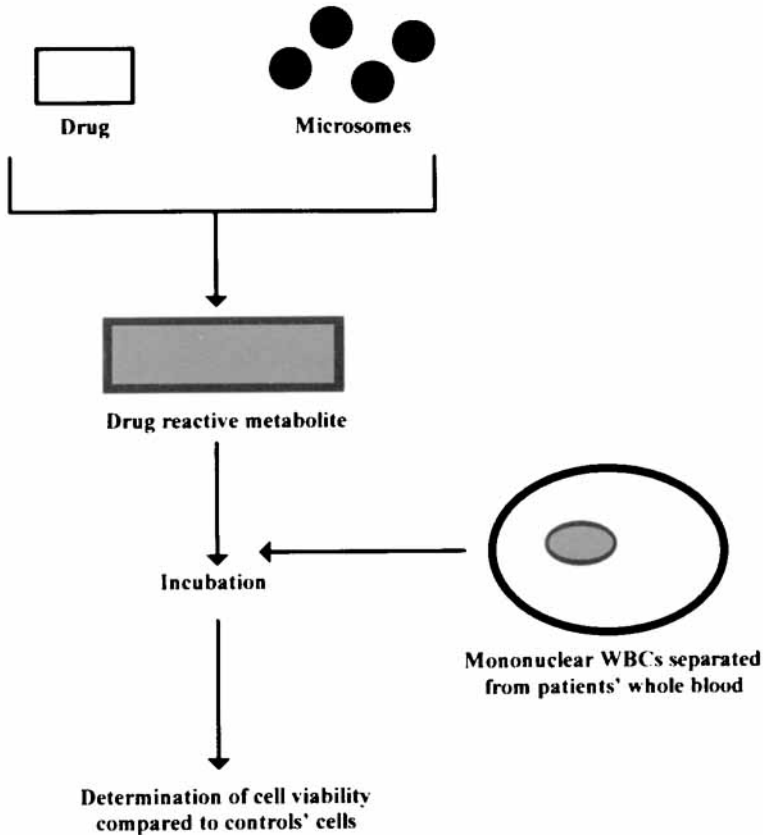


Figure 2. Leukocyte toxicity assay using murine microsomes as a source of cytochrome P450 enzymes that convert a drug to its cytotoxic metabolite in genetically susceptible patients. The resulting cell death correlates with the patient's drug hypersensitivity.

sitivity reactions are often characterized by the development of high fever and severe skin rash after 10 to 14 days of therapy.⁴⁰ The rash is often severe, and is either toxic epidermal necrolysis that is life-threatening or erythema multiforme. Approximately 25% of patients also have involvement of the heart, liver, kidneys or bone marrow. These reactions have been associated with a 30% to 50% mortality rate, often secondary to infectious complications of exfoliative dermatitis.⁴⁰ This assay has also been used to study serum-sickness-like reactions to cefaclor.³³

The leukocyte infotoxicity assay reliably identifies individuals genetically at risk for cytotoxic drug reaction syndromes. It is critical to use appropriate positive and negative controls. The assays are research tools and not widely available. The specificity, sensitivity, and predictive value of these assays is unknown.

Computer-Assisted Evaluation of Adverse Events Using a Bayesian Approach

Computerized decision aides have been developed and are under investigation in the medical field of diagnostic and therapeutic decision making. With the understanding that the differential diagnosis of adverse drug reactions is complex (because for each adverse event there are many possible drug and nondrug causes), a computerized, user-friendly diagnostic aid for Bayesian assessment of adverse drug events has been developed.³⁶

There are three different inferential bases that have been applied to medical decision making using computers: algorithms, statistical methods (includes Bayes theorem), and artificial intelligence. Of the second group, the most common statistical method for differential diagnosis has been the Bayesian model. This model takes an initial probability estimate and uses additional patient-specific information to modify risk probability and calculate the likeliest diagnosis.

The Bayesian adverse reaction diagnostic instrument (BARDI) is explicit in the information that is used and how each piece of information is weighted, and uses Bayesian statistics to combine factors coherently.³⁶ The Bayesian method can include any relevant information and can consider multiple possible causes. Testing has shown that BARDI is valid.^{36, 46}

A prototype computer program called Mac BARDI-Q&A has been developed to calculate the odds in favor of a particular drug causing an adverse event compared with an alternative cause. These odds are referred to as the posterior odds.³⁶ The posterior odds factor is calculated by considering six assessment subsets: one deals with background, epidemiologic or clinical trials information (i.e., the prior odds), and the other five deal with case-specific information (i.e., the likelihood ratios). The prior odds factor is the ratio of the expected drug-attributable risk and the background risk of a certain adverse event in a population sharing basic characteristics with the patient being considered (such as medical condition). The five likelihood ratios deal with any information of differential diagnostic value under the categories of patient history; timing of the adverse event with respect to drug administration; characteristics of the adverse event; drug dechallenge, which refers to any signs, symptoms, or occurrences after drug withdrawal; and a drug rechallenge or readministration of the suspected causal drugs. The product of these factors is the posterior odds.³⁶

This computer-assisted evaluation of adverse drug events needs further study and validation, but results to date look encouraging.⁴⁶ As further informa-

tion is gained in medical literature, this can be entered into existing data banks, hopefully improving the accuracy of the computer-assisted diagnosis of adverse and immunologic drug reactions.

CONCLUSION

Properly diagnosing adverse drug reactions, although often complicated and difficult, is important for patient and clinician. Often the question of whether it is safe to readminister a medication in the future is an important clinical judgment that needs to be made. Alternative medications may be less effective or have greater toxicities or cost.

Areas of ongoing active research to improve diagnostic precision for allergic drug reactions include further understanding the immunochemistry of allergenic medications, improving the reproducibility and sensitivity of relevant in vitro assays, and further validating computer-assisted evaluation of adverse drug events. The positive and negative predictive values for these diagnostic tests ultimately needs to be better defined where possible. At the present time, the primary diagnostic tool for properly assessing immunologic drug reactions remains a meticulous and detailed history obtained by an astute, knowledgeable, and motivated physician.

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