Articles

Recognizing and Reporting Adverse Drug Reactions

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Although physicians in practice are most likely to see patients with adverse drug reactions, they may fail to recognize an adverse effect or to attribute it to a drug effect and, when recognized, they may fail to report serious reactions to the US Food and Drug Administration (FDA). To recognize and attribute an adverse event to a drug effect, physicians should review the patient's clinical course, looking at patient risk factors, the known adverse reactions to the suspected drug, and the likelihood of a causal relationship between the drug and the adverse event—based on the temporal relationship, response to stopping or restarting the drug, and whether other factors could explain the reaction. Once an adverse drug reaction has been identified, the patient should be informed and appropriate documentation made in the patient's medical record. Serious known reactions and all reactions to newly released drugs or those not previously known to occur (even if the certainty is low) should be reported to the FDA.

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Although physicians in practice are those most likely to encounter cases of adverse drug reactions, they may fail to recognize them or to attribute an adverse event to a drug effect. Even if recognized as a possible drug reaction, such events are rarely reported. In one study, only 57% of practicing physicians surveyed were familiar with the US Food and Drug Administration's (FDA) voluntary reporting system. Although more than 400 physicians thought that they had detected a serious case of an adverse drug reaction within the past year, only 21 had actually reported it.[1] The purpose of this communication is to review the classification and recognition of these events and to provide practical information on the reporting requirements and process.

Recognizing Adverse Drug Reactions

Adverse drug reactions occur in about 10% of patients admitted to hospital, and 3% to 6% of hospital admissions are related to an adverse drug event. These figures are rough estimates because of the variability in the recognizing and reporting of these events by physicians and are probably low. Comparable data on adverse drug reactions in the outpatient setting are not available. An adverse drug reaction has been defined by the World Health Organization as "one which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."[2] Karch and Lasagna modified this definition to exclude therapeutic failures.[3] The FDA uses a definition that in addition addresses reactions resulting from overdose, drug withdrawal, and therapeutic failures and that may be too broad to be clinically useful.

TABLE 1.—*Severity of Adverse Drug Reactions*

Mild
Does not require treatment or hospital admission or prolong a hospital stay
Moderate
Requires treatment
Requires hospital admission or prolongs a hospital stay by at least a day
Severe
Is life-threatening
Contributes to the death of the patient
Is permanently disabling
Requires admission to a critical care unit
Takes longer than 2 weeks for recovery
Causes a neoplastic process

Adverse drug reactions can be classified according to severity—that is, whether the reaction requires treatment, necessitates hospital admission, or is life-threatening (Table 1). They can also be classified by mechanism: Type A reactions involve exaggerated pharmacologic responses (such as β-blocker–induced congestive heart failure), and type B reactions, which are idiosyncratic and unpredictable based on a drug's pharmacology, may be immunologically mediated (such as carbamazepine-induced thrombocytopenia).

The likelihood that an adverse event is related to drug therapy is classified as definite, probable, possible, or doubtful. The probability classification is based on the temporal relationship of drug administration and the reaction, whether the reaction is a known consequence of the drug, if the reaction resolved on stopping the drug to determine its association with a reaction or recurred with reinstituting the drug to see if the reaction reappears, and if the patient's clinical state could explain the reaction (Table 2). Not all adverse drug reactions fit neatly into one category or another, and clinical judgment is often necessary to determine probability. Various methods for determining the probability of drug reactions have been published. The algorithm developed by Naranjo and colleagues provides a simple method for scoring reaction characteristics and is frequently used.[4] Other more complex methods, such as the method described by Venulet and co-workers, weigh various contributing factors and address concurrent diseases such as renal or hepatic dysfunction.[5] There has been no comparison of these various methods.

Although premarketing clinical trials frequently last several years and involve hundreds of patients, they cannot ensure complete safety of a new drug. Often premarketing trials

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ABBREVIATIONS USED IN TEXT

FDA = US Food and Drug Administration
JCAHO = Joint Commission on Accreditation of Healthcare Organizations

fail to detect serious but rare drug reactions, delayed effects associated with long-term use, adverse effects in selected subgroups of patients (such as geriatric or pediatric populations) or associated with specific diseases, or drug–drug interactions. For these reasons, postmarketing surveillance is essential for both evaluating drugs marketed less than three years—the period during which a drug is termed a new chemical entity by the FDA—and monitoring the frequency of known drug reactions. The single most important way to identify these clinically significant reactions is the recognition and voluntary reporting of them by physicians.

To recognize and attribute an adverse event to a drug effect, physicians should review the patient's clinical course, looking specifically at pertinent characteristics of the patient and drug, as well as the reaction itself, to assess the likelihood of a causal relationship between the drug and the adverse reaction (Table 3). In particular, the patient's concurrent medication, significant medical problems, and risk factors for adverse reactions should be evaluated. The patient's medication regimen should be carefully screened and the patient queried about all medications taken, including over-the-counter and medications "borrowed" from others, to ensure accurate identification of the causative agent. The reaction that occurred should be evaluated in light of the patient's clinical state as well; could the event be explained by known characteristics of the patient's medical illnesses?

Risk factors for adverse drug effects in hospitalized patients include a serious underlying illness or infection, abnormal renal or hepatic function, a previous adverse drug reaction, or multiple drug therapy.[6] Age may not be an independent risk factor but may relate to other factors, such as multiple drug therapy or altered metabolism and excretion of medication. The use of multiple drugs has been the risk factor most strongly and consistently correlated with adverse drug reactions; the rate of such reactions climbs from about 4% in patients receiving 1 to 5 drugs to about 24% in those receiving 11 to 15 medications. It also contributes to drug–drug interactions, which should be ruled out whenever an adverse reaction is suspected. In addition, the use of newly marketed drugs may be a risk factor, as experience with their use is understandably limited compared with drugs in long-term clinical use.

TABLE 2.—*Probability of Adverse Drug Reactions*

Definite
Follows a reasonable temporal sequence after a drug is given or from the time the drug concentration has been established in body fluids or tissues
Follows a well-known response pattern to the suspected drug
Lessens or disappears on stopping the drug (dechallenge)
Reappears if the drug is restarted (rechallenge)
Probable
Follows a reasonable temporal sequence after a drug is administered
Follows a known response pattern to the suspected drug
Lessens or disappears on stopping the drug
Cannot be explained by the patient's underlying clinical state
Possible
Follows a reasonable temporal sequence after a drug is given
Possibly follows a known pattern to the suspected drug
Could be explained by the patient's underlying clinical state or other factors or modes of therapy administered to the patient
Doubtful
Does not follow a reasonable temporal sequence after a drug is given
Can likely be explained by the patient's underlying clinical state or other factors or modes of therapy administered to the patient

TABLE 3.—*Characteristics Helpful in Attributing an Adverse Event to a Drug Effect*

Patient characteristics
Concurrent prescription and nonprescription medications
Serious medical problems
Risk factors for adverse drug reactions, including patient age, serious underlying illness, infection, abnormal renal or hepatic function, previous drug reaction, or multiple drug therapy
Suspected drug reaction characteristics
Drug name or manufacturer
Dosage and duration of therapy
Type of reaction that occurred
Literature or FDA documentation of side effects or adverse reactions to the suspected drug
*Likelihood of a causal relationship between the drug and the adverse event**
Temporal sequence of the reaction following drug administration
Whether the reaction was a known adverse event to the suspected drug
Whether the causal relationship between the reaction and the suspected drug was confirmed by dechallenge or rechallenge; what was the patient outcome
If the reaction could be reasonably explained by known characteristics of the patient's clinical state

FDA = US Food and Drug Administration

*See Table 1 for probability classification.

Once a suspected drug is identified, known adverse reactions to this drug should be reviewed and compared with the type of reaction that occurred and with the clinical result. Certain classes of medications may be more commonly associated with adverse drug reactions. Table 4 lists these drugs along with the types of reactions most frequently reported. After this information is gathered, the probability of the event being an adverse drug reaction can be assessed.

The clinician can facilitate the process of identifying an adverse drug reaction by eliciting information and assistance from pharmacists, pharmaceutical manufacturers, and the FDA and by doing a literature search of case reports and pharmacoepidemiologic studies. Also, similar reactions reported with other drugs in the same or a similar class may be helpful. Pharmacists are often able to identify possible drug reactions, as they may be the first ones contacted about a reaction by either patients in the ambulatory care setting or nurses in hospitals. By screening the medication profile, pharmacists can identify drugs most likely to cause an adverse reaction and can also provide a valuable resource through their access to current drug information. Useful references include Davies's *Textbook of Adverse Drug Reactions*,[7] D'Arcy and Griffin's *Iatrogenic Diseases*,[8] Duke's *Meyler's Side Effects of Drugs*,[9] and the manufacturer's product information, which can be found in the package insert or a current *Physicians' Desk Reference*.[10] The Drugdex Drug Information System, available on microfiche or CD-ROM computer disk, is also a succinct source of information. Pharmaceutical manufacturers provide updated information reported on their products as well.

Example of Adverse Drug Reactions

Case 1

The patient, a 64-year-old man with left lower extremity cellulitis who was allergic to penicillin, had the development

TABLE 4.—Adverse Drug Reactions Most Frequently Reported

Drug categories most frequently reported
Antibiotics
Analgesics, including nonsteroidal anti-inflammatory agents
Cardiac drugs
Antihypertensive agents
Asthma drugs
Types of reactions most frequently reported
Dermatologic
Neurologic
Gastrointestinal
Cardiac
Pulmonary
Ear, nose, and throat or mouth

of facial flushing and edema and moderate bronchospasm after receiving 300 mg of vancomycin hydrochloride intravenously over 35 minutes. The infusion was stopped, and intravenous diphenhydramine hydrochloride and methylprednisolone sodium succinate, as well as subcutaneous epinephrine, were administered. The symptoms resolved completely within four hours. This patient had the skin manifestations characteristic of the "red neck syndrome," known to occur with intravenous vancomycin use. The red neck syndrome is directly related to the rate of infusion and most frequently occurs when the drug is infused rapidly, within an hour. The reaction appears to be the result of vasodilation due to the release of histamine. Because of the temporal relationship between administering the drug and the reaction and the pronounced similarity to other previously reported, well-known reactions with the drug, it was considered a definite adverse reaction of moderate severity, despite the fact that a rechallenge was not done.

Case 2

Several hours after receiving 1 gram of vancomycin and 100 mg of gentamicin sulfate intravenously, a 40-year-old man with an infected arteriovenous fistula shunt had a bright red, pruritic, diffuse maculopapular rash develop on his trunk and extremities. The patient had received both drugs a week previously without incident. Despite treatment with intravenous diphenhydramine, the rash worsened and the skin desquamated, requiring a course of oral prednisone before his symptoms resolved. Causality was less clear in this case, in which a reaction developed after two different drugs were given in close temporal proximity. Although allergic reactions manifesting as rash are more common with the use of vancomycin than with gentamicin, a definite association with one agent could not be made, and the reaction was considered a probable adverse reaction of moderate severity to either vancomycin or gentamicin.

Case 3

The patient, a 64-year-old man with hypertension, was prescribed mexiletine hydrochloride for symptomatic ventricular tachycardia. Shortly afterward, he had an episode of excessive blood pressure elevation with readings of 220/115 to 130 mm of mercury, which returned to 122/76 mm of mercury after the drug was discontinued. Two days after rechallenge with mexiletine, his blood pressure again rose to 220/115 mm of mercury and again returned to normal after the drug was stopped. A workup was negative for pheochromocytoma, and mexiletine was investigated as a cause of his hypertension. A review of the literature and consultation with the manufacturer elicited no reports of hypertensive exacerbation or reactions with the use of mexiletine or any other antiarrhythmics. A follow-up of this case revealed several later episodes of comparable blood pressure elevation while off mexiletine therapy. Although his hypertension was closely associated with mexiletine administration, and there was an apparent rechallenge that produced similar results, the labile hypertension later demonstrated by this patient precluded its designation as a definite drug reaction. Because of these doubts and the lack of similar reactions described in the literature, this hypertensive reaction was labeled as a possible adverse drug reaction of moderate severity and was reported to both the drug manufacturer and the FDA.

Reporting Adverse Drug Reactions

Once an adverse drug reaction is identified, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires that the reaction be documented in the patient's medical chart and that it be reported by the clinician or other health care professional such as a nurse or pharmacist. The JCAHO has required all hospitals to develop a system to summarize adverse drug reactions, to observe for trends that occur in in-hospital patients or outpatients in affiliated clinics, and to conduct ongoing drug utilization monitors. The lack of a reporting system for adverse drug reactions was the second most frequently cited deficiency in hospitals in 1989-1990. Physicians can report such reactions in hospitalized patients to a designated hospital committee—an adverse drug reaction, pharmacy and therapeutics, quality of care, or risk management committee assigned to this function—and hospital pharmacists can assist in this process. The designated hospital committee should then forward appropriate reports to the FDA.

Physicians can also contact the drug manufacturer about a possible adverse drug reaction and receive information on other similar reactions to the suspected drug. Phone numbers for medical information services of pharmaceutical manufacturers are available in the *Physicians' Desk Reference* or through local pharmaceutical representatives. Drug manufacturers are required by law to forward information about possible adverse drug effects to the FDA.

The FDA has a voluntary reporting system for detecting adverse events after a drug has been released for clinical use (postmarketing drug surveillance). Physicians, pharmacists, and even nonhealth professionals can report possible reactions to the FDA directly, and the FDA can provide information on whether similar reactions have been reported previously. It is especially important to report drug reactions in outpatients (as well as in patients in hospital if the hospital's designated committee does not forward its reports to the FDA). An Adverse Reaction Reporting form can be obtained from a local FDA office; a separate form is available for reporting adverse events to vaccines through the FDA's Vaccines Adverse Event Reporting System. Additional information can be obtained from the FDA's national toll-free number, 1-800-638-6725. The voluntary act of reporting cases does not increase physicians' medicolegal liability, as the name of the reporting physician is held in confidence and is not subject to release under the federal Freedom of Information Act.

Physicians should report to the FDA any possible adverse event where there is strong suspicion that a drug involved is producing the event—the physician need not be certain

that the drug is the cause—and when the event is serious (Table 1).

Known reactions that are serious should be reported to the FDA, but all unexpected reactions need to be reported. All reactions to newly released drugs (marketed for less than three years) need to be reported as well. It is not necessary to report therapeutic failures, poisoning or suicide attempts, overdoses due to dosage or administrative error, or a mild reaction not requiring treatment.

Physicians can also submit unusual drug-induced reactions as case reports to medical journals to heighten awareness of a rarely seen or newly recognized adverse drug event. In contrast to single case reports, pharmacoepidemiology, the study of the use and effects of drugs in large numbers of persons, will have an increasing influence on clinical medicine, through both clinical studies of postmarketing drug evaluation and JCAHO-required hospital committees on adverse drug reactions.[1]

Ethical and Medicolegal Implications of Adverse Drug Reactions

Physicians have the responsibility to use their clinical skills to detect adverse drug reactions and then to act on that information. A physician must decide whether an adverse event was indeed a drug reaction, based on the reaction itself and known reactions to the suspected drug; we do not advocate rechallenge in most patients. Readministering a suspected drug when a possible drug reaction has occurred is a decision that a physician must make based on the type and severity of the adverse event and the likelihood that this was a drug reaction. There are no known standards specifically designed to direct physicians in this ethical decision. Once an adverse event has been attributed to a drug reaction, the patient should be informed of it, and JCAHO standards require documenting the reaction in patients' medical records.

For serious drug reactions, documentation in the progress notes is not enough; the information should be listed on a problem list, by a "drug alert" sticker on the chart, or on a computerized medication profile. Reporting the event to the FDA is voluntary; it is the physician's ethical responsibility to learn about the reporting system and how and what to report.

Summary

Physicians should be aware of the potential for adverse drug reactions, especially in high-risk patients, and should be able to attribute an adverse event to a drug effect. Physicians should familiarize themselves with the FDA reporting form, keep a supply on hand, and send a completed form to the FDA to report a suspected drug reaction. If a physician does not have time to report to the hospital, the manufacturer, and the FDA, the FDA should be selected (unless the hospital committee reports drug reactions to the FDA for its physicians). Physicians should be encouraged to report all serious drug reactions, even if the certainty is low, because the FDA will follow up the reports and obtain additional information if it receives a number of reports of suspected reactions of low certainty. Erring on the side of overreporting allows the FDA to assemble the data needed to detect adverse drug reactions. Such reporting, particularly of newly released drugs, is the responsibility of health care professionals in all clinical settings.

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