A MEDWATCH Continuing Education Article

Provided as a service by the Staff College, Center for Drug Evaluation and Research, Food and Drug Administration June 1995

Clinical Therapeutics and the Recognition of Drug-Induced Disease

Physicians and other health professionals should be aware of the extent and spectrum of drug-induced disease. Monitoring for and reporting adverse events can save lives and spare others from illness.

Learning Objectives:

Upon completion of this program, health professionals should be able to:

- Understand the importance of postmarketing drug surveillance
- Identify basic limitations of premarketing clinical trials in the detection of adverse drug reactions
- Explain how the pharmacokinetic and pharmacodynamic properties of a drug influence its efficacy and expected toxicity
- List the types of adverse drug reactions
- Describe the thought process involved in recognizing an adverse drug event (ADE)
- Differentiate which ADEs to report to the Food and Drug Administration's (FDA) MEDWATCH program

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In 1989, a 39-year-old woman was admitted to a hospital because of a series of episodes of syncope and light-headedness that had started two days prior to admission. Ten days earlier she had been prescribed terfenadine and cefaclor for recurrent sinusitis. She was also taking medroxyprogesterone for menorrhagia. On the eighth day of therapy, because of early symptoms of vaginal candidiasis, she discontinued the cefaclor and began self-medicating with ketoconazole.

In the hospital she was diagnosed with torsades de pointes, a rare life-threatening ventricular arrhythmia that is most commonly drug-induced. Lab tests done by the drug manufacturer revealed elevated levels of unmetabolized terfenadine, a compound not usually detectable due to extent of metabolism.[1] It was subsequently discovered that the ketoconazole inhibited the oxidative metabolism of terfenadine, thereby allowing an accumulation of the drug.[2] Cardiotoxicity had already been reported to be associated with terfenadine overdose,[3] but not with therapy at normal doses.

In everyday clinical practice, adverse events associated with the use of medical products can lead to hospitalization, permanent disability, and even death. Each year ADEs, such as the case scenario described above, are the cause of significant morbidity and mortality. While most adverse events are predictable and can be anticipated, others are unpredictable, especially rare fatal idiosyncratic reactions.

Articles reviewing the numerous studies of the occurrence of adverse effects report that between 3% and 11% of hospital admissions could be attributed to adverse effects.[4] The chance a patient will experience an ADE during hospitalization ranges from 1% to 44%,[5,6] dependent on the type of hospital, definition of an adverse event, and study methodology.[7] A substantial portion of ADEs are potentially avoidable.[8,9]

Any drug can conceivably have toxic or undesired effects. In an effort to increase health professionals' awareness of the extent of drug and device-induced disease, the Commissioner of the Food and Drug Administration (FDA) announced in June 1993 the launch of MEDWATCH , an initiative designed both to educate physicians and other health professionals about the critical importance of being aware of, monitoring for, and reporting adverse events; and to facilitate reporting directly to the FDA.[10]

Premarketing Studies

Although FDA has one of the most rigorous preapproval processes in the world, clinical trials cannot uncover every safety problem, and they are not expected to do so.

Due to the limited size and controlled nature of premarketing clinical trials (See TABLE 1), only the most common adverse events (i.e., those occurring more frequently than 1 in 1000 exposures) will be observed and subsequently listed in the product's official labeling at the time of approval. Clinical trials seldom detect, or define the frequency of, all important adverse events.

For example, when the new anticonvulsant felbamate was first marketed in September 1993, aplastic anemia had not been detected during the clinical trials; however, by July 1994, nine cases had been reported in an estimated 100,000 patients in the United States, the majority of whom had been exposed for less than one year. Given that aplastic anemia is rare, with a reported background rate of two to five cases per million persons per year,[11] the case rate in felbamate users represented a great increase (50 fold or more) over the expected rate.[12]

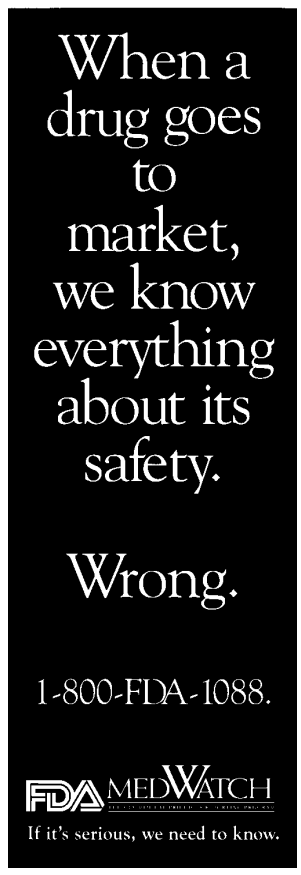
Clinical trials are effective tools primarily designed for assessing efficacy and risk-benefit ratio, but in most cases they are neither large enough nor long enough to provide all information on a drug's safety. At the time of approval for marketing, the safety database of a new drug will often include 3,000 to 4,000 exposed individuals, an insufficient number to detect rare adverse events. For example, in order to have a 95% chance of detecting an adverse event with an incidence of 1 per 10,000 patients, an exposed population of 30,000 patients would be required.[13]

Although most drugs are studied for up to ten years prior to marketing, an individual clinical trial usually involves patient exposure of less than a year. Even the longest duration trials, which can last several years, expose patients for less time than what will occur postmarketing with a chronically administered agent. Moreover, clinical trials are usually too short to detect adverse events with long latency. Because of these limitations, it is only after a product is marketed and widely used that a more complete safety profile emerges.

TABLE 1

Limitations of Premarketing Clinical Trials

- Short duration — effects that develop with chronic use or those that have a long latency period are impossible to detect
- Narrow population — generally don't include special groups (e.g., children, elderly), to a large degree, and are not always representative of the population that may be exposed to the drug after approval
- Narrow set of indications — those for which efficacy is being studied and don't cover actual evolving use
- Small size (generally include 3,000 to 4,000 subjects) — effects that occur rarely are very difficult to detect



Furthermore, as new drugs enter the marketplace, the potential for interactions with other drugs, medical devices and foods increase. **Concomitant use of drugs, medical devices, and other products must be continually evaluated in the presence of new drug therapies for possible adverse events.**

Pharmacology of Adverse Drug Events

The same pharmacologic mechanisms that account for a drug's efficacy account for many of its toxic effects, as most drug-induced adverse events are expected extensions of a drug's known pharmacologic properties.[14] Thus, detailed knowledge of a drug's pharmacology will help in assessing for possible adverse effects. For example, with the cardioselective beta blockers (e.g., atenolol), both the bradycardia side effect and the therapeutically desired reduction in blood pressure are mediated through the drug's effect on the beta-1 adrenergic receptors.

For many therapeutic agents, there is a relatively wide range in the dose of drug required to produce a response, either toxic or therapeutic, in different individuals. Many therapeutic agents exhibit a dose-response curve which is linear over a wide range, so that an increase in dose will produce a proportional increase in the measured response. However, at higher doses, the dose-response curve tends to plateau (reach maximum effect) and further increases in dose in this range usually result in increased frequency and severity of ADEs without added benefit.

In certain situations the safe and effective therapeutic range of a drug may become narrower. Factors that may cause narrowing include age, sex, individual pharmacokinetic or pharmacodynamic sensitivity, underlying disease, and concomitant medications. **For these reasons, knowledge of the pharmacokinetic and pharmacodynamic properties of a drug and its pharmaceutical formulation can help predict what adverse events might be expected.** If the way the body handles a drug is abnormal (a pharmacokinetic change), or if genetic factors or underlying disease alter the sensitivity of target organs to the drug (a pharmacodynamic change), then the patient's response to the drug, even when prescribed in a normal manner, can be exaggerated (or in some cases, reduced).

Pharmacokinetics

Pharmacokinetics represents what the body does to a drug. It describes individual variability in the plasma concentration of a drug over time due to

differences in absorption, distribution, metabolism, and excretion of the drug. Higher plasma unbound drug concentrations can result from an increased absorption rate, displacement of drug from plasma protein binding sites, inhibition of usual drug metabolic rate, or reduced renal excretion. The rate of absorption is one of the most important contributors to a higher maximum concentration of a drug given orally; peak concentrations are often key to both a drug's efficacy and its potential toxicity. Differences in both the extent and rate of absorption may have profound therapeutic implications. The absorption rate can be influenced by the timing of meals and the type and amount of food eaten, as well as by other drugs taken within 30-60 minutes. Gastrointestinal motility and the state of the mucosa can also alter absorption.

The distribution of a drug will influence eventual plasma level dependent on regional blood flow; extent of red blood cell and plasma protein binding; and the drug's intrinsic ability to cross cell membranes.

Alterations in drug elimination rates are probably the most important cause of pharmacokinetic ADEs.[14] Almost all drugs are excreted in the urine or bile, or metabolized by the liver to active or inactive metabolites which are then excreted by the kidneys. A decrease in the elimination rate can cause toxicity due to an elevated plasma concentration; increasing the elimination rate can result in a lack of drug effect due to reduced plasma concentrations. Diseases of the liver and kidney can be expected to impair drug elimination. Cardiac disease can often result in reduced metabolic activity in general because of poor oxygenation and organ perfusion. Genetic factors such as enzymatic polymorphism can influence the rate of metabolism, as with fast and slow metabolizers through the hepatic cytochrome P450 (CYP2D6) enzyme system, which affects the metabolism of fluoxetine. Similarly, polypharmacy can give rise to ADEs when two drugs that are metabolized by the same pathway are given concurrently, causing a rise in the plasma level of the one that "loses" the competition [e.g., terfenadine interaction with ketoconazole or erythromycin within the P450 (CYP3A4) enzyme pathway].

Pharmacodynamics

Pharmacodynamics represents what the drug does to the body. It includes the mechanisms of drug action and seeks to relate the plasma drug concentration to the drug effect. Some ADEs are due to differing sensitivity to the drug at the target site; individuals with the same serum drug levels may well experience different degrees of ADE intensity when on the same drug (e.g., dystonia secondary to neuroleptics). It is not known why some patients respond differently to a given drug level, but evidence is mounting that tissue sensitivity is impacted by the drug receptors themselves, by physiological homeostatic mechanisms, and by the disease state of the individual.[14]

Understanding the pharmacodynamic mechanism of action of drugs helps to explain and predict multiple and diverse end organ toxicities of many drugs. An illustrative example is the group of nonsteroidal anti-inflammatory drugs (NSAIDS), which, through their actions on the prostaglandin system, can induce adverse drug effects on the kidney, circulating platelets and the gastrointestinal tract.

An application of pharmacodynamic principles in clinical therapeutics is the effort to maximize efficacy and minimize toxicity of drug combination therapy for such serious disorders as cancer, severe hypertension, major bacterial infections and the prevention of transplant rejection. The underlying rationales for using drugs with different mechanisms of action include promotion of synergistic beneficial pharmacologic effects; avoidance of overlapping and/or additive side effects by dose reductions; and prevention of the emergence of drug resistance.

Types of Adverse Drug Events

Drug-induced adverse events can range from mild side effects to very severe reactions, including death. Classification of ADEs into predictable (Type A) or unpredictable (Type B) toxicity, while not entirely satisfactory due to possible clinical overlap, is a generally accepted, simple way of looking at this issue.[14]

Type A (predictable) events

Type A reactions are expected extensions of an individual drug's known pharmacologic properties and are responsible for the bulk of ADEs encountered. These events may represent an excess of the pharmacologic effect (e.g., hypotension with antihypertensive agents), or may be due **not** to the primary pharmacologic action that mediates the drug's therapeutic effect, but rather to a secondary pharmacologic property it possesses (e.g., anticholinergic effects with the tricyclic antidepressants). Type A reactions are usually dose-dependent and predictable, but can be due to concomitant disease, drug-drug, or drug-food interactions. **Even though their incidence and morbidity is high, they are rarely life-threatening, although they can produce significant disability.** Most Type A events are identified prior to marketing and listed in a product's labeling. However, as the previously cited interaction between terfenadine and ketoconazole demonstrates, sometimes very important drug-drug interactions are not detected prior to marketing.

Type A ADEs due to pharmacokinetic differences commonly disappear when concentrations in plasma are reduced. **Ways to minimize both pharmacokinetically- and pharmacodynamically-derived ADEs include understanding the pharmacology of the drug being prescribed, monitoring drugs with a narrow therapeutic window (see TABLE 2), and avoiding polypharmacy whenever possible.**

Type B (unpredictable) events

Type B reactions include idiosyncratic reactions, immunologic or allergic reactions (e.g., anaphylaxis), and carcinogenic/teratogenic events. Unlike Type A reactions, they are usually **not** an extension of the known pharmacological activity of the drug, seeming to be more a function of patient susceptibility than the intrinsic toxicity of the drug. Type B reactions are rarely predictable or avoidable and are generally independent of the dose and route of administration.

These reactions seem to concentrate in certain body systems; while liver, blood and skin are most commonly affected, the kidney, nervous system, and other body systems may also be targets.[15] **Type B reactions, while uncommon, are often among the most serious and potentially life-threatening of all ADEs, and are a major cause of important drug-induced disease.** Yet, in most cases, the mechanisms involved are unknown.[15]

Certain rare events are known to be drug-induced much of the time. For example, about 20-30% of hepatic failure cases are drug-induced according to one literature review,[16] while drug-induced hematologic toxicity leading to thrombocytopenia, hemolytic anemia, agranulocytosis or aplastic anemia is well-documented. Aplastic anemia occurs rarely, but one author's literature-based estimate is that between one-third to two-thirds of all cases are related to drug treatment.[17] Similarly, the most severe type of skin reactions, (erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) are frequently drug-induced, with an outpatient rate due to drugs of 7.0, 1.8, and 9.0 per 10^6 person-years respectively.[18]

Type B events, with the exception of immediate hypersensitivity reactions like anaphylaxis, generally require a minimum of 5 days of treatment before cells become hypersensitive to the drug but there is no maximum time for reactions to occur (although most will have occurred by 12 weeks).[19] Some events may be delayed a long time, making it possible for an ADE to appear after drug therapy has been discontinued (e.g., clear cell adenocarcinoma in female offspring of DES users).

CASE STUDY:

NSAIDS in a Geriatric Patient

PRESENTING HISTORY

A 68 year old mildly obese female with known hypertension and adult onset diabetes mellitus presents to the emergency room (ER) complaining of chest pain and shortness of breath (SOB) of 3 days duration. She is currently taking digoxin, hydrochlorothiazide (HCTZ), potassium chloride (KCl), cimetidine, tolazamide for 1 year and a new analgesic nonsteroidal anti-inflammatory drug (NSAID) called "ALLPROFEN" for low back pain for the past 5 days. (Note: "ALLPROFEN" is a hypothetical new analgesic.) The patient has no known drug allergies. Her physical exam is unremarkable except for a presystolic cardiac extra sound (S4). Her blood pressure is 150/90 sitting, heart rate is 80 and regular. ECG shows LVH and nonspecific ST-T wave changes.

List at least four major possible etiologies for chest pain in this patient.

1. [Cardiac origin, e.g., coronary artery disease (CAD) or congestive heart failure. The patient has a history of hypertension and adult onset diabetes which are major risk factors for CAD. In addition, she is taking digoxin and HCTZ consistent with previous history of congestive heart failure.]
2. [Noncardiac musculoskeletal chest wall pain.]
3. [Noncardiac pain originating from the gastrointestinal tract which can present as chest pain similar to cardiac disease. This includes hiatal hernia with reflux esophagitis-gastritis, etc. related to previous disorder (the patient is on cimetidine) or a new problem related to the new NSAID.]
4. [Pulmonary embolus.]

List at least three important points (positive or negative) that should be ascertained from this patient's history regarding chest pain.

1. [The PQRST symptom analysis for pain. This includes questions about Provocative-palliative factors, Quality, Region, Severity, and Temporal characteristics of pain.][26]
2. [Prior history of similar symptoms and clinical course (diagnosis and treatment).]
3. [If a specific disease entity is suspected, e.g., CAD or gastroesophageal reflux disorder, other pertinent points might include family history of similar disorder and compliance with current drug regimen related to cimetidine.]

TABLE 2

Therapeutic Drug Monitoring

When prescribing drugs, it should be kept in mind that pharmacokinetic variability means that one dose does not always fit all. Some adverse reactions are currently preventable by rational use of therapeutic drug monitoring (TDM), which individualizes doses by taking into account important patient variables. TDM is only of value in preventing reactions related to serum concentrations.

For certain drug classes, pharmacokinetic variability together with a narrow therapeutic index have led to a standard dosing strategy utilizing TDM to ensure safe use and avoid excessive toxicity, to the degree possible. Drugs that should be routinely monitored include digoxin, lithium, lidocaine, aminoglycosides, aminophylline, phenytoin, cyclosporine and tacrolimus.

Doses need to be individualized (adjusted up and down) to get patients within the desired therapeutic range. For many of these agents, clinical/laboratory monitoring of relevant pharmacodynamic endpoints is also recommended in conjunction with TDM (e.g., monitoring renal function in an aminoglycoside-treated patient.)

Recognizing an ADE

Consideration of drugs as disease and symptom producing agents should always be incorporated into the formulation of a differential diagnosis. A complete drug history, including nonprescription drugs, is critical to this process.

When faced with a suspected ADE, it is important to try to determine the background symptom incidence rate before making a judgement about the event, as placebos and even no treatment can be associated with adverse events. In one clinical study 58% percent of subjects receiving a placebo complained of one or more "side effects" during treatment.[20] The complaints reached the point that blinded nurses finally urged discontinuation of treatment due to the apparently toxic effects of the medication. Another study found 81% of presumably healthy people who were taking no medication had symptomatic complaints that often are assumed to be drug-induced, such as fatigue, inability to concentrate and excessive sleepiness.[21]

Recognizing ADEs is vitally important but highly subjective and imprecise. Defining the relationship between drug exposure and the occurrence of an event is not easy, and it is often impossible to reach a firm conclusion. In one study, three clinical pharmacologists were asked to evaluate 60 cases to determine whether medication, alcohol or recreational drug use had caused hospitalization.[22] In 63% of the cases, there was major disagreement as to whether

any agent was implicated and there was complete agreement between the clinical pharmacologists and the treating physicians less than half the time.

Since ADEs may act through the same physiological and pathological pathways as normal disease, they are difficult and sometimes impossible to distinguish. However, the following step-wise process (steps 1-6[23]) may be helpful in assessing for a possible drug-related adverse event:

1) Ensuring the drug ordered is the drug received;

2) Ensuring the drug was actually taken;

3) Verifying that the onset of the event was **after** the drug was taken, not before;

4) Determining the time interval between the beginning of drug treatment and the onset of the event;

5) Dechallenging - stopping the drug and monitoring the patient's status, looking for improvement;

6) Rechallenging - if appropriate, restarting the drug and monitoring for recurrence of any adverse events. **N.B.** There is always the possibility that the initial exposure to the drug desensitized the patient and there will be no ADE the second time around.

7) Using personal experience as a clinician and relevant literature about drugs and ADEs. The manufacturer of the drug can also be a resource to consult. Most companies list a toll-free phone number in the Manufacturer Index Section of the *Physicians' Desk Reference*. However, Type B reactions occur rarely and corroboration through clinical experience or the medical literature is difficult, if not impossible;

CASE STUDY (cont'd):

NSAIDS in a Geriatric Patient

HOSPITAL/HOME COURSE

She is admitted to the CCU for further observation. The ER physician decides to maintain all of her current medications but to discontinue the new NSAID. The patient does well clinically over the next 24 hours. The cardiac enzymes are normal and the ECG remains unchanged. The patient is then discharged home on her regular medications except for the new NSAID. At home, the back pain returns 3 days later. She decides to restart the ALLPROFEN and goes to bed. Within 1 hour after taking this medication, she develops dyspnea, wheezing, tightness and pain in the chest which radiates to the left shoulder and down her arm.

She returns to the ER. The exam is essentially unchanged from her previous visit except for some bibasilar rales. Her BP is 160/95. Heart rate is 90 and regular. ECG shows ST-T wave changes consistent with ischemia.

List your top two etiologies for chest pain and dyspnea.

1. [Ischemic heart disease secondary to CAD.]
2. [An ADE associated with ALLPROFEN. This is somewhat problematic given the temporal sequence. One general mechanism for NSAID -induced ADEs relates to their pharmacologic effect (inhibition of prostaglandins) on the kidney leading to sodium and fluid retention. This could theoretically precipitate congestive heart failure and lead to nocturnal angina pectoris. It is doubtful, however, that a single dose could produce this effect. However, more plausible could be an allergic pulmonary drug reaction which could account for the SOB and wheezing. The patient may have taken NSAIDs in the past. Allergic reactions with NSAIDs are thought to involve several mechanisms including pharmacologically mediated reactions and an immune response to a chemical antigen or cross-sensitization (i.e., classical anaphylaxis).]

If your list included an adverse drug reaction, what should you do, if anything?

1. [Treat the patient symptomatically for ischemic heart disease. In addition, supportive therapy including nasal oxygen and possible diphenhydramine should be considered for the possible allergic drug reaction.]
2. [Check relevant drug information sources such as the PDR for previous reports of allergic reactions associated with ALLPROFEN.]
3. [Report this possible allergic drug reaction to your hospital drug monitoring committee even if you are not sure that it was definitely an adverse drug reaction.]

TABLE 3

Report Serious Adverse Events To MEDWATCH

- By Mail: Use the postage-paid MEDWATCH form†
- By Phone: 1-800-FDA-1088
- By Fax: 1-800-FDA-0178
- By Modem: 1-800-FDA-7737

† Available from hospital pharmacies or by calling 1-800-FDA-1088

8) Being aware of drug-drug, drug-food, and drug-device interactions, as many patients, especially in hospitals, are taking multiple medications;

9) Quantifying the drug levels if at all possible - some drugs will remain in the body for weeks after the drug is stopped.

Reporting Adverse Drug Events

The FDA has the regulatory responsibility for ensuring the safety of all marketed drugs. Drug manufacturers are required by federal regulation to notify the FDA of all adverse events of which they are aware[24]; however, to do so, they first need to find out about them. Unfortunately, many physicians do not think to report ADEs either to the manufacturer or to the MEDWATCH program* at FDA.

Most hospitals maintain some type of ADE surveillance system to qualify for accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). JCAHO standards establish concurrent ADE monitoring as a function of both the pharmacy department and the Pharmacy and Therapeutics (P & T) Committee. In addition, the JCAHO requires that hospitals promptly report "significant" reactions to the FDA.[25] These institutional systems are also dependent on active participation by physicians.

While quality assurance concerns are a motivation for monitoring all ADEs in the hospital, the FDA does not want a report on every ADE encountered; this is not practical for reporters nor useful to the FDA. Reporters should be selective in their reporting. **The key to reporting to MEDWATCH is to remember that FDA is particularly interested in SERIOUS adverse events (both Type A and Type B.)**

FDA considers an event serious if the patient outcome is a death, life-threatening event, hospitalization (initial or prolonged), disability, congenital anomaly, or if medical or surgical intervention was required to prevent permanent damage. Stopping drug therapy, changing the dosage, and treatment with a prescription drug are not in themselves considered serious. **It is not necessary to prove causality—a suspected possible association is sufficient reason to report.**

By concentrating on reporting serious events, health professionals can help the FDA focus efforts on events with the most significant public health impact. Reports may be sent to the FDA either via the manufacturer or directly by several different mechanisms (see TABLE 3).

Based on careful analysis of these reports, FDA can take various actions which include sending out "Dear Health Professional" letters; requiring labeling, name or packaging changes; conducting further epidemiologic investigations; requiring manufacturer-sponsored postmarketing studies; conducting inspections of manufacturers' facilities/records; and requiring actual withdrawal of the drug from the market, when necessary (e.g., temafloxacin in 1992).

Confidentiality

FDA recognizes that the confidentiality of the identities of both reporters and patients is an important concern of health care providers. The patient's identity is held in strict confidence by the FDA and is protected to the fullest extent of the law. FDA also protects the identity of all reporters in order to encourage the reporting of serious adverse events and medication errors. Unless indicated otherwise on the reporting form, a reporter's identity may be shared with the manufacturer of the product. Nevertheless, FDA will **not** disclose a reporter's identity in response to a request from the public under the federal Freedom of Information Act.

* MEDWATCH is the FDA Medical Products Reporting Program for health professionals to report serious adverse events and product problems that occur with all medical products including drugs, biologics, medical devices and special nutritional products (e.g., medical foods, dietary supplements and infant formulas).

Summary

Recognition of drug-induced disease is of critical importance in the course of clinical practice. **Including a possible ADE or drug-drug interaction in the differential diagnosis of a patient's disease or clinical symptoms, and considering these factors in the work-up, should become part of the regular diagnostic thought process.**

Timely reporting of serious adverse events is critical to an effective national postmarketing surveillance program. Knowledge of a drug's safety profile continually evolves over the product's lifetime, with the growth of this knowledge base contingent on active participation by physicians and other health-care professionals. Without this information, FDA is hindered in its efforts to assure the safety of marketed medical products.

Toward this end, participation in the MEDWATCH program should be viewed as an integral part of every clinician's professional and public health responsibility. Such participation can help save lives, reduce suffering and decrease health care costs through improved patient care and clinical therapeutics.

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

If it's serious, we need to know.

CASE STUDY (cont'd):

NSAIDS in a Geriatric Patient

SUBSEQUENT COURSE

The patient is started on several new medications including nitroglycerin and an ACE inhibitor. She is told to discontinue the NSAID and to take acetaminophen prn for back pain.

Six months later, the patient undergoes arthroscopic chondroplasty and a partial meniscectomy of the left knee under epidural anesthesia with 2% mepivicaine. The anesthetic wears off and she complains of throbbing knee pain 2 hours after the procedure. She receives ketorolac 30 mg IM with prompt relief. Thirty minutes later the patient is discharged, but collapses in the hospital lobby. The hospital administrator who happens to be in the lobby calls "code blue". The code team arrives and finds the patient unresponsive, cyanotic, hypotensive (BP-50/30) with urticaria and a palpable carotid pulse of 80.

List the two most likely causes of her problem.

1. [Anaphylactic shock secondary to ketorolac. The constellation of sudden collapse associated with hypotension, wheezing, and urticaria is classic. However, if urticaria was not present, then an acute MI would be a real possibility.]
2. [Acute MI with cardiogenic shock.]

An airway is established and she is started on O_2 with positive pressure ventilation. She regains consciousness and begins to wheeze. Epinephrine (1 mg) is administered followed by IV fluids. By the next day, the patient is stabilized with return of her usual blood pressure and normal breathing. You now think that the above syndrome of sudden collapse associated with hypotension, urticaria and wheezing 30 minutes after taking ketorolac may be drug related but you are not sure.

What are your responsibilities to report this suspected ADE to your hospital monitoring committee?

[Clearly, this serious reaction needs to be reported even if you are not absolutely sure it was caused by the drug in question.]

What should the hospital monitoring committee do about reporting this suspected ADE?

[Clearly, this serious reaction should be reported to MEDWATCH/FDA. This is true even if this kind of anaphylactic reaction has been documented in the PDR and thus is a known ADE of ketorolac.]

Acknowledgements

We would like to acknowledge the editorial input of Richard M. Kapit, M.D., Sandra L. Kweder, M.D., Thomas P. Laughren, M.D., and Robert C. Nelson, Ph.D.

This continuing education article is based in part on the June 10, 1994 MEDWATCH Conference on the Management of Drug-Induced Disease sponsored by FDA and Georgetown University, Washington, DC.

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SELF-ASSESSMENT QUESTIONS

This program is sponsored by the Center for Drug Evaluation and Research (CDER), Food and Drug Administration.

CDER is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. The Center designates this program for 2 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

CDER is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education (ACPE Universal Program No. 181-601-95-090). This program meets the ACPE criteria for .2 continuing education units (2 contact hours) in pharmaceutical education.

To receive certification of continuing medical education credit or pharmaceutical education credit the participant must:

- Answer at least 7 of the 10 self-assessment questions correctly
- Provide the required information on the answer sheet below
- Participants receiving a failing grade will be notified

NOTE: THIS PROGRAM EXPIRES ON DECEMBER 31, 1996

1. Postmarketing drug surveillance is important because premarketing clinical trials are
   a. not able to detect ADEs that occur rarely
   b. not able to detect ADEs with long latency periods or those that occur with chronic therapy
   c. not able to predict all potential drug-drug interactions
   d. all of the above

2. In most cases premarketing clinical trials cannot detect adverse drug events that occur less frequently than
   a. 1 case in 10 patients (10% incidence rate)
   b. 1 case in 100 patients (1% incidence rate)
   c. 1 case in 1,000 patients (0.1% incidence rate)
   d. 1 case in 10,000 patients (0.01% incidence rate)

3. Which of the following statements about the clinical pharmacology of ADEs is false:
   a. if rechallenge with a drug suspected of having caused an ADE does not produce the ADE in question, it is safe to conclude that the ADE and drug are not associated
   b. an ADE can result when two drugs used for two different indications compete for the same metabolic pathway, such as terfenadine and ketoconazole
   c. patient factors such as renal or hepatic function can have major impact on the development of an ADE
   d. an ADE can result at the same dose in one patient and not in another because of genetic differences in the rate of metabolism

4. Which of the following does NOT represent pharmacokinetic variation among individuals?
   a. differences in the rate of absorption
   b. differences in the distribution of a drug
   c. differences in the elimination rate
   d. differences in response at a given drug plasma level

5. Which of the following represents an example of pharmacodynamic variation among individuals?
   a. there may be anywhere from a 10-30 fold interindividual difference in the serum blood levels achieved with the same dose of a drug
   b. elderly patients can often be more sensitive to adverse events, even at the same steady-state blood levels for a drug, than younger patients
   c. differences in creatinine clearance between individuals may necessitate use of different doses of a renally-cleared drug to achieve the same steady-state blood level
   d. differences in the rate of drug metabolism between fast and slow metabolizers in the hepatic P450 (CYP2D6) system

6. Which of the following describes a Type A (predictable) adverse drug event?
   a. usually dose-dependent and an extension of the known pharmacology of the drug
   b. high incidence
   c. most are identified prior to marketing and listed in a product's labeling
   d. all of the above

7. Which of the following does NOT describe a Type B (unpredictable) adverse drug event?
   a. frequently detected during premarketing clinical trials
   b. occur rarely and are usually unavoidable
   c. generally independent of dose and route of administration
   d. usually the most serious and life-threatening of all ADEs

8. Which of the following rare events are known to often be drug-induced?
   a. hepatic failure
   b. thrombocytopenia, hemolytic anemia, agranulocytosis, and aplastic anemia
   c. erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis
   d. all of the above

9. Of the following, which would be of important consideration in assessing a patient for an ADE?
   a. time course on the suspected agent
   b. knowledge of the patient's complete drug history, including nonprescription drugs
   c. previous exposure to the suspected agent
   d. all of the above

10. Which of the following does NOT apply when reporting ADEs to the FDA MEDWATCH program?
    a. Only SERIOUS ADEs should be reported [i.e., if the patient outcome is death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or if medical or surgical intervention was required to prevent permanent damage]
    b. causality need not be proved before submitting a report to the FDA
    c. all ADEs, serious or otherwise, detected through a JCAHO required hospital ADE monitoring system should be reported to the FDA
    d. ADEs may be reported to the FDA through the manufacturer who is required by federal regulation to send them to the Agency

DRUG-INDUCED DISEASE

MEDWATCH

APPLICATION FOR CONTINUING EDUCATION CREDIT
ANSWERS:

1._____ 2._____ 3._____ 4._____ 5._____ 6._____ 7._____ 8._____ 9._____ 10._____

Date:_____ Phone number:_____

Name:_____ Degree:_____

Address:_____

City:_____ State:_____ Zip:_____

The article met the stated learning objectives.

_____ Strongly Agree _____ Agree _____ Disagree _____ Strongly Disagree _____ Cannot Decide

The information presented is relevant to my clinical practice. _____ Agree _____ Disagree

❑ Please send me a copy of The FDA Desk Guide for Adverse Event and Product Problem Reporting (contains forms and instructions).

Mail the completed answer sheet by December 31, 1996 to:

MEDWATCH, HF-2, Rm 9-57, FDA, 5600 Fishers Lane, Rockville, MD 20857 or FAX it to 1-800-FDA-0178.