

MEDICAL COLLEGE OF GEORGIA

The following courses will be offered by the College in July: "Clinical Genetics" (July 7-9); and "Medical Oncology and Hematology — Recent Advances" (July 9-12).

Contact the Div. of Continuing Education, Medical College of Georgia, Augusta, GA 30912-6450; or call (404) 828-3967.

PULMONARY CIRCULATION

A course entitled "Pulmonary Circulation in Health and Disease" will be offered at the Wisconsin Center in Madison, July 8-11.

Contact Sarah Z. Aslakson, Continuing Medical Education, University of Wisconsin, 465B WARF Bldg., 610 Walnut St., Madison, WI 53705; or call (608) 263-2856.

CALL FOR PAPERS

Abstracts are now being accepted for the second International Conference on Pharmacoepidemiology, entitled "Population Based Data Systems Linking Drugs, Medical Care and Disease," to be held in Minneapolis, September 10-12. The deadline for receipt of applications is July 1.

Contact Dr. Stanley A. Edlavitch, Div. of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN 55455; or call (612) 624-4426.

UNIVERSITY OF SOUTHERN MAINE

The University will offer a course entitled "Curriculum for the Hearing Impaired" at the Governor Baxter School for the Deaf on Mackworth Island, Me., July 7-11.

Contact Barbara McGough, University of Southern Maine, 400 Bailey Hall, Gorham, ME 04038; or call (207) 780-5326.

SPECIAL REPORT

ADVERSE-DRUG-REACTION MONITORING

THE U.S. Food and Drug Administration (FDA) has long been conducting a program to monitor reported adverse drug reactions to approved drugs. The purpose of this paper is to review the rationale for monitoring adverse drug reactions, to describe the current program, and to encourage physician participation in the program. The program began in the late 1950s, after the registration by the American Medical Association of cases of aplastic anemia due to chloramphenicol.¹ It expanded greatly when the 1962 revision of the Food and Drug Act required the pharmaceutical industry to report adverse drug reactions to the FDA. Since 1969, data from the program have been entered into a computer, and more than 280,000 reports have accumulated in the data base. In recent years, the discovery of major safety problems after marketing, as in the cases of zomepirac (Zomax) and benoxaprofen (Oraflex), has led to increased attention to the monitoring of adverse drug reactions.

BACKGROUND

Pharmaceutical products undergo extensive and costly testing and review before marketing. Approval for marketing is primarily based on well-controlled clinical trials to demonstrate efficacy and safety. Thus, when the marketing of a drug begins, there is already considerable evidence that it will be useful while not causing unacceptable harm.

However, it must be recognized that preapproval testing cannot provide complete assurance of safety or information about all effects. This is because of several practical limitations in the conduct of human trials.^{2,3} Such trials seldom involve more than 2000 patients or last longer than three years. Thus, they may not detect very uncommon side effects⁴ (e.g., anaphylaxis caused by zomepirac⁵) and delayed effects of long-term administration (e.g., cervical cancer associated with the use of oral contraceptives⁶). Important adverse reactions discovered after marketing may occur at a rate of 1 in 10,000 prescriptions (e.g., pseudomembranous colitis following the use of lincomycin⁷) or less. Most patients enrolled in clinical trials have relatively uncomplicated disease and are drawn from restricted age groups. Thus, preapproval data often do not apply to pregnant women, children, elderly persons, and patients with complicated diseases who require treatment with multiple drugs. Yet, these groups may well be exposed to a drug after marketing begins.

Because of the inherent shortcomings of preapproval clinical trials, postmarketing surveillance is crucial for providing additional safety information that cannot be realistically collected before approval of the drug.⁸⁻¹³ "Surveillance" in this context may be defined as the systematic detection of drug-induced reactions by practical, uniform methods. Its overall purpose is to provide new information on drug risks, and it includes the analysis of collected data and the dissemination of this information. Data from surveillance of the actual use of drugs in medical practice are routinely used as a basis for modifications in drug usage and for making new estimates of risk. One key aspect of postmarketing surveillance is the maintenance of a system for the reporting of adverse drug reactions.

The collection and analysis of reports on adverse drug reactions is important because such reports provide early warnings of previously undetected, serious drug risks. If such monitoring had been done in Europe in the late 1950s, the discovery of teratogenicity due to thalidomide¹⁴ would have occurred much earlier than it did. Analyses of the adverse-reaction monitoring program at the FDA have shown that it can generate postmarketing data as effectively as can many structured and costly postmarketing studies.^{15,16} It has been noted that "most unexpected ADRs [adverse drug reactions], in fact, are turned up by voluntary reporting" and that "reporting by physicians remains the single most important source of suspected ADRs."⁸ Lasagna recently stated, "Spontaneous reporting by the alert and competent doctor will, for the foreseeable future, remain the most important source of new leads about drugs."¹⁷

STRUCTURE OF THE ADVERSE-REACTION MONITORING PROGRAM

FDA monitoring of adverse reactions is primarily based on "spontaneous" reports from practicing physicians — i.e., reports that originate from observations

made in the usual practice of medicine (not derived from a formal study). Spontaneous reports reach the FDA through either the drug manufacturers or direct contact by physicians. When a physician notifies a manufacturer about a possible reaction, the manufacturer is required by law and regulations¹⁸ to report this observation to the FDA. Direct reporting to the FDA is encouraged by the distribution of a report form that is mailed to nearly all physicians in the United States several times a year in the *FDA Drug Bulletin*.

For an adverse-reaction report to be interpretable, it must contain descriptions of the reaction, the exposure to the drug, the temporal relation between exposure and reaction, and the underlying disease. When the FDA receives a report, it assigns standard terms to the description of the reaction¹⁹ and enters the report into its computer data base. Every direct report from a physician and all manufacturers' reports of unexpected serious reactions are individually reviewed. The review includes a check to determine whether the reaction is already listed in the drug's package insert, an assessment of the severity of the reaction, and a preliminary assessment of the probability that the reaction was related to the drug exposure. For screening purposes, a reaction is generally considered serious if it resulted in death or hospitalization. When the reaction is deemed serious, the possibility of such a reaction had not been mentioned on the package insert, and the reaction may be related to the exposure to the drug, the computer file is searched for similar reactions. After consultations with epidemiologists, pharmacologists, and others, decisions are made about the degree of intensity of follow-up.

Detailed analyses are carried out for reactions that may indicate important, previously unknown risks. These analyses may include the development of a profile of all reported reactions to the specific drug involved, calculation of reporting rates relative to use of the drug, comparisons with adverse-reaction profiles of other drugs in the same therapeutic class, an examination of premarketing adverse-reaction data, and quantitation of the relation of the drug to the reaction, with the use of epidemiologic data bases.

In addition to reviews of individual reports, quarterly and annual tabulations are done for recently approved drugs and for drugs that are a source of suspicion. These compilations are analyzed for patterns of concern.

SUMMARY OF 1984 ADVERSE-REACTION REPORTS

In 1984, 26,753 spontaneous adverse-reaction reports from individuals or manufacturers in the United States were received by the FDA. Ninety percent of these reports came through manufacturers, and the rest came directly from health care providers. Twenty-four percent of the reported reactions were classified as serious because they involved hospitalization (18 percent) or death (6 percent).

Between 1980 and 1983, 41 drugs that were classified as new chemical entities were initially marketed

and were each prescribed at least 100,000 times, according to the National Prescription Audit (purchased from IMS America, Ambler, Pa.), or were used frequently in hospitals. Of the 26,753 reports in 1984, 5230 (20 percent) identified 1 of the 41 new chemical entities as the suspect agent. Since about 85 million prescriptions were written for these 41 drugs, whereas about 1.5 billion prescriptions were written for other drugs, the adverse-reaction reporting rate for the new drugs (62 per million prescriptions) was four times higher than that for other drugs (15 per million prescriptions). The severity of the reactions described in the reports on the new drugs did not differ substantially from that mentioned in the reports on other drugs (Table 1). In addition, little difference in the description of the severity of the outcome of reactions to the new drugs was found in comparisons between direct reports from physicians and those from manufacturers. Zomepirac and benoxaprofen have been excluded from these analyses because the reporting patterns for those agents were atypical.

An analysis of the distribution of adverse-reaction reports according to the therapeutic class of the suspect drug and the extent of its use was revealing. In an evaluation that employed the FDA groupings of therapeutic classes, it was found that the distribution of adverse-reaction reports roughly parallels the extent of use of the drugs, as derived from evaluation of the National Prescription Audit, except in the case of the nonsteroidal antiinflammatory drugs (Fig. 1; "Arthritis" column). These agents accounted for 21 percent of the adverse-reaction reports but for only 5 percent of outpatient prescriptions. This may be partly explained by intensive manufacturer surveillance and reporting on drugs in that therapeutic class.

USES AND LIMITATIONS OF DATA ON ADVERSE DRUG REACTIONS

National surveillance of adverse reactions is a complex process because of the volume of drugs involved and the need to assess causality and risk. Nearly 1.6 billion prescriptions for more than 30,000 drugs are written each year in the United States (National Pre-

Table 1. Distribution of Spontaneous Adverse Drug-Reaction Reports on New Chemical Entities, According to Origin and Reaction Outcome.*

OUTCOME OF REACTION	ORIGIN OF REPORT		
	MANUFACTURER	HEALTH CARE PROVIDER	TOTAL
	no. (%)		
Hospitalization, no death mentioned	889 (18)	87 (22)	982 (19)
Death, with or without hospitalization	222 (5)	20 (5)	243 (5)
No mention of hospitalization or death	3703 (77)	296 (73)	4005 (76)
Total	4814 (100)	403 (100)	5230 (100)

*Figures are from 1984 reports in the United States. The source is the Office of Epidemiology and Biostatistics, U.S. Food and Drug Administration.

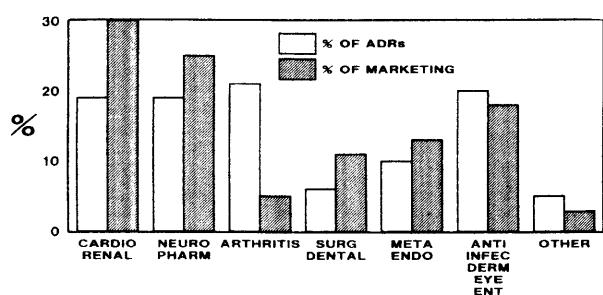


Figure 1. Percentage Distribution of Reports on Adverse Drug Reactions (ADRs) and Market Share of Drugs in 1984, According to Therapeutic Class.

scription Audit), and about 200 new prescription drugs are approved. About 20 of these approved drugs are new chemical entities; the remainder are reformulations and other modifications of known chemicals.

In spite of this complexity, the monitoring of spontaneous reports has, at times, directly resulted in changes in recommendations for use and drug availability. Generally, the reactions involved in such instances are distinct clinical entities that are reported at rates much higher than expected. Recent examples include teratogenesis caused by isotretinoin (Accutane)²⁰ and toxic epidermal necrolysis associated with pyrimethamine-sulfadoxine (Fansidar).²¹ Other examples of adverse reactions that were discovered by means of spontaneous reports include phenformin-induced lactic acidosis,²² hepatic tumors associated with oxymetholone,²³ and hepatic failure associated with ticrynafen.²⁴

Adverse-reaction monitoring can also provide a profile of the types of reactions that may be occurring to one drug or a group of drugs. For example, analyses of reports on nonsteroidal antiinflammatory drugs show that rates of hematologic reactions are higher for oxyphenbutazone and phenylbutazone than for other such drugs.²⁵ Similarly, the highest proportion of anaphylactic reactions to nonsteroidal antiinflammatory drugs occur with benoxaprofen and zomepirac.

A third use of data on adverse drug reactions is to provide information on patient risk factors. For example, most reports that have associated aplastic anemia with phenylbutazone involved elderly women; this association was confirmed in an epidemiologic study by Inman.²⁶

Despite their usefulness, one or even many reports of adverse reactions often do not provide sufficient information to confirm that a drug caused the reaction.²⁷ A reaction may be caused by the suspect drug, another drug that a patient is taking, or the underlying diseases for which the drug was prescribed; it may also be entirely coincidental.²⁸ Thus, adverse-reaction monitoring should be viewed primarily as a means for identifying potential problems. Confounding is particularly likely when the drug exposure and the outcome are relatively common. In the case of doxylamine-pyridoxine (Bendectin), for example, there were large

numbers of reports of congenital defects associated with exposure to the drug, simply because there was widespread use of the drug during pregnancy; the coincidental, noncausal nature of the association appears to have been demonstrated.²⁹

A further limitation of the use of adverse-reaction data results from the underreporting of reactions and the various biases that affect reporting. Medical or mass media attention can stimulate reporting in a distorted manner. In addition, some adverse reactions are more likely to be diagnosed and reported than others because of their known associations with drugs. For example, aplastic anemia is far more likely to be attributed to a drug exposure and reported than is a more common disorder, such as myocardial infarction. For these reasons, it has to be remembered that reporting rates do not necessarily reflect occurrence rates. Consequently, reliable risk estimates cannot usually be made from spontaneous adverse-reaction data alone.

Postmarketing monitoring of adverse reactions should be viewed as one component of pharmacoepidemiology.³⁰ Both monitoring and epidemiology are based on the nonexperimental collection of observed data on exposure and outcome. Interpretation of adverse-reaction data, like interpretation of other epidemiologic information, must take into account the rates of exposure and possible confounding factors. Often, possibilities derived from reaction monitoring must be tested with use of analytical epidemiologic techniques, including case-control and cohort studies.^{31,32}

EFFECT OF ADR REPORTING

How is information on adverse drug reactions actually used? After sufficient evidence is gathered, several mechanisms are employed to modify prescribing practices. New information may be added to the package insert of the product to guide providers.¹⁶ In other instances, the availability of the product may be restricted because of either voluntary withdrawal from the market (as occurred with zomepirac)⁵ or recall (as in the case of phenformin).²² Dissemination of new safety information also occurs by means of the *FDA Drug Bulletin* and the medical literature.

There is no fixed formula for regulation of drug safety because risks must always be balanced against benefits. The severity of the disease being treated and the availability of alternative therapy must be considered. In the case of isotretinoin, for example, how should the risk of teratogenesis be weighed against disfiguring acne and its attendant psychological effects? These are not easily resolved issues, but the starting point is to gather data on risks and benefits. The FDA uses its internal staff and advisory committees to analyze these data and determine appropriate action.

ROLE OF THE PHYSICIAN

Ultimately, the value of any surveillance system is determined by the nature and volume of the reports it

receives. The rate of adverse-reaction reporting in the United States is far below that in many other developed countries.³³ To improve reporting, revised regulations¹⁸ and guidelines have clarified reporting requirements and procedures for manufacturers. The FDA has also sponsored pilot studies in Maryland and Rhode Island that are aimed at stimulating direct reporting by physicians.

Physicians in practice must recognize that all the effects of new drugs have not been elucidated at the time of marketing. Much of the development of knowledge about adverse effects depends on the ability of individual physicians to detect these effects and to make preliminary attributions to the drug when appropriate. The FDA and the medical community share the responsibility for providing continual evaluation of drug performance after marketing. If the medical community and patients are to benefit from the experience of individual physicians, suspected reactions must be reported.^{34,35} Indeed, "supplying information on suspected adverse reactions is as much a moral duty for the physician as are other aspects of patient care."³⁶ This is particularly true in the case of serious reactions to new drugs, regardless of whether such reactions have been mentioned in the package inserts.

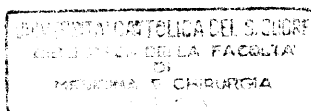
A number of factors may inhibit physicians from reporting adverse reactions they have observed.³⁷ The most important may be the lack of knowledge that a reporting program exists and the lack of readily available report forms. Physicians are urged to keep blank copies of the report form that is mailed to them by the FDA. Another inhibition may be concern about possible litigation related to an adverse-reaction report. However, it must be remembered that the adverse-reaction surveillance program is designed to detect possible safety problems with drugs and that the submission of a report does not constitute a legal claim or an acceptance of causality. Because the identities of the reporters and the patients are kept confidential by the FDA, individual reports have little value in the courtroom. The desire to publish may also inappropriately inhibit early reporting to the FDA. Authors are urged to send in early notification of adverse reactions to the FDA, while articles are being prepared or are in press.^{34,38} Physicians need to be assured that their reports are important and that they are used.³⁹

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