

SPECIAL ARTICLE

THE DISCOVERY OF DRUG-INDUCED ILLNESS

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Abstract The increased use of drugs (and the concurrent increased risks of drug-induced illness) require definition of relevant research areas and strategy. For established marketed drugs, research needs depend on the magnitudes of risk of an illness from a drug and the base-line risk. With the drug risk high and the base-line risk low, the problem surfaces in premarketing studies or through the epidemic that develops after marketing. If the drug adds slightly to a high base-line risk, the effect is undetectable. When

both risks are low, adverse effects can be discovered by chance, but systematic case-referent studies can speed discovery. If both risks are high, clinical trials and nonexperimental studies may be used. With both risks intermediate, systematic evaluations, especially case-referent studies, are needed. Newly marketed drugs should be routinely evaluated through compulsory registration and follow-up study of the earliest users. (N Engl J Med 296:481-485, 1977)

THE increase in the use of drugs for both short-term and long-term treatment during the past decades has led to a corresponding increase in concern about their potential for inducing serious illnesses.* As a result, the search for drug-induced disorders has achieved a high priority in medical research.^{1,2}

In many cases the identification of drug induction of illnesses is straightforward and can be accomplished readily by informal clinical observation. Rapid discovery of a drug-illness relation tends to occur when the induced illness is dramatic and occurs within a very short period after a drug is taken — for example, penicillin-induced anaphylaxis and ethacrynic-acid-induced deafness. When a drug produces such reactions frequently, the problem is likely to be recognized during premarketing studies, and the drug may not be approved for routine clinical use. However, when a drug produces such an illness only rarely, the discovery of the adverse effect is more likely to occur in the post-marketing period, after widespread clinical use.

Under other circumstances, drug induction of serious illness may not be recognized through informal clinical experience. Clinical observation tends to be insufficient when the time necessary to induce the illness is long — weeks, months or years — especially when the drug induces the illness only rarely or when the illness is otherwise reasonably common (or both). In these circumstances, the use of formal methods rather than reliance on clinical observations is required.

With these considerations in mind, my purpose is, first of all, to delineate the areas of need for formal research into potential relations between drugs and illness, and secondly, to propose guidelines for the choice of research strategy.

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*Illnesses that are potentially life threatening or otherwise produce substantial incapacity, disability or both. Many examples are given in the paper.

The problem of drug-induced illness can be defined by the magnitudes of two risks — the added risk of illness experienced by users of a drug, and the base-line risk in the absence of the drug. Somewhat arbitrarily, each risk is taken to be “high” if the rate of newly occurring illness exceeds one per 200 per year, “low” if less than one per 10,000 per year and, otherwise, “intermediate.” Table 1 lists various combinations of these magnitudes of risk. For the resulting categories, the need for formal research is determined not only by the likelihood that drug-illness relations will be missed during the process of informal clinical observation, but also by the nature of illnesses that in each category are particularly apt to be drug induced.

The strategy for research includes several basic approaches. The options are the following: *clinical trial* — an experimental study in which patients are randomly assigned for the duration of the study to one of the compared treatments and are followed forward in time, for some defined period, to ascertain the possible development of illnesses; *nonexperimental cohort study* — a follow-up study in which the choice of drug regimen is dictated by ordinary clinical practices rather than the interest of scientific comparison; and *case-referent (“case-control”) study* — a study in which patients with an illness of interest are compared to a series of people without the illness for the proportions who have and have not used any of the drugs of interest.

DRUG COMMONLY INDUCES AN OTHERWISE RARE ILLNESS (CATEGORY 1, TABLE 1)

In this situation the rate of drug induction of a given illness is “high,” and the base-line rate is low.

Need for Research

When a drug commonly induces an otherwise rare, serious illness, the likelihood is very high that the problem will be discovered in the premarketing phase. In the extraordinary circumstance in which premarketing observation fails to discover the adverse effect, as in the thalidomide disaster, discovery after marketing is likely to occur through informal clinical ob-

Table 1. Types of Drug-Illness Relations.

| CATEGORY | RATE OF ILLNESS* | | EXAMPLE | PRIMARY MODE OF DISCOVERY | RESEARCH APPROACH OF CHOICE | | ILLNESSES OF PARTICULAR INTEREST |
|----------|------------------|--------------|--|---|--|----------------------------------|--|
| | DRUG INDUCED | BASE LINE | | | DRUGS ALREADY MARKETED | NEWLY MARKETED DRUGS | |
| 1 | High† | Low‡ | Thalidomide-induced phocomelia | Clinical observation | Case referent | "Cohort" | Any rare illness |
| 2 | Low | High | — | Not discoverable | — | — | — |
| 3 | Low | Low | Chloramphenicol-induced aplastic anemia | 1: Clinical observation 2: Formal research | Case referent | "Cohort" | Any rare illness |
| 4 | High | High | ? Tolbutamide-induced cardiovascular mortality | Formal research | 1: Clinical trial 2: Case referent 3: "Cohort" | 1: Clinical trial 2: "Cohort" | Myocardial infarction & sudden deaths in high-risk populations |
| 5 | Intermediate | Intermediate | Estrogen-induced endometrial cancer | Formal research | Case referent | "Cohort" | Particular cancers |

*Refers to acquired illness only.

†Arbitrarily defined as $>1/200/\text{yr}$ for the purposes of this paper.

‡Arbitrarily defined as $<1/10,000/\text{yr}$ for the purposes of this paper.

servation: after the necessary lag time since the introduction of the drug, a dramatic epidemic develops whose detection, although somewhat delayed, requires no formal study. An extraordinarily high proportion of the patients will have a positive history of exposure to the causative drug, and this distribution leads to the rapid identification of the drug-illness relation. Because such drug-illness connections are so readily and quickly identified when they are fully manifested, it is unlikely that any adverse effects of this kind exist undiscovered for drugs already on the market. Of course, if the lag time is appreciable, recognition of an adverse effect is correspondingly delayed.

Although the needs for formal post-marketing research are minor in this category, virtually any rare illness is a potential candidate for drug induction.

Strategy for Research

Although it is exceptional for a drug to be marketed if it commonly induces an otherwise rare, serious illness, it is of interest to consider how the effect, when it occurs, may be discovered. When the phocomelia epidemic of the early 1960's became evident,³ its cause was sought by the case-referent approach: a series of cases of phocomelia was contrasted to healthy babies for the frequency of various prenatal experiences. In the case series a far greater proportion of mothers had taken thalidomide early in pregnancy as compared to the mothers of normal babies. Thus, it was inferred that the risk of phocomelia was very much higher in the offspring of thalidomide-using mothers than in the others. In general, the potential drug causation of an unexplained epidemic of illness is most efficiently evaluated by the case-referent approach.

The existence of Category 1 side effects of newly marketed drugs is ruled out by premarketing studies. In the extraordinary case in which they have not, untoward reactions will come to attention rapidly upon the development of the epidemic. Consequently, no

special follow-up effort is indicated for Category 1 drug illnesses.

DRUG RARELY INDUCES AN OTHERWISE COMMON ILLNESS (CATEGORY 2, TABLE 1)

When an illness is rarely induced by a drug and is common in its absence, the proportion of cases due to the drug is very small; neither general clinical experience nor formal research will identify the drug-illness relation. For example, if the incidence of an illness were one per 100 per year in the absence of drug treatment and the drug itself induced the illness in one per 50,000 per year, the risk among the users would be increased only to 1.002 per cent. Weak relations of this kind simply will have to remain undiscovered.

DRUG RARELY INDUCES AN OTHERWISE RARE ILLNESS (CATEGORY 3, TABLE 1)

There are many known examples in this category. Among the more familiar ones are the connection between chloramphenicol and aplastic anemia,⁴ oral contraceptives and benign liver tumors,⁵ practolol and sclerosing peritonitis,⁶ lincomycin and pseudomembranous colitis,⁷ and diethylstilbestrol and vaginal cancer.⁸

Need for Research

Drug-illness relations in this category almost always escape notice in the premarketing phase since a vast experience is needed before cases of the rare illness occur. On the other hand, once experience has accrued after marketing, informal discovery of the problem is likely, particularly when a drug accounts for a large proportion of the rare illness. However, even when a relation is recognized by chance, the discovery is always delayed. Reduction of this delay is the major objective of formal research.

As previously noted, virtually any rare illness may be suspected of having been drug induced.

Strategy for Research

An example of a formally discovered relation in Category 3 is the connection between maternal use of diethylstilbestrol and vaginal cancer in the offspring.⁸ A series of eight cases of this exceedingly rare condition was accrued and contrasted to a series of 32 normal girls. Detailed histories for a number of etiologic factors were taken in each series. Of the eight patients with cancer, seven had a history of intrauterine exposure to diethylstilbestrol in contrast to none in the reference series.

For the discovery of drug-illness relations in this category, the case-referent approach is particularly feasible in the study of drugs already on the market because an appreciable number of cases of the rare illness have to accumulate. Since any given case-referent study focuses on a single illness only, separate series for each of the rare illnesses of concern need to be assembled to explore the role of drug exposure fully.

For newly marketed drugs, some kind of monitoring scheme is needed to uncover adverse effects early. The most efficient means of monitoring newly marketed drugs for rare, serious toxicity might be to establish a central registry of a large number of the earliest patients who receive the drug and to follow up these patients at periodic intervals for the development of serious, unusual illness. Users of new drugs could be inexpensively and rapidly identified if notification of use (by the prescribing physician or by the pharmacist who filled the prescription) to a central registry was mandatory and automatic. Periodic follow-up observation of users with mailed questionnaires that inquire about the development of serious illness should identify most drug-illness connections within the first few cases, particularly if the illness is otherwise rare and dramatic.

DRUG COMMONLY INDUCES AN OTHERWISE COMMON ILLNESS (CATEGORY 4, TABLE 1)

An example of the high risk associated with a drug when the risk of an illness in the absence of the drug is also high is the putative effect of tolbutamide in increasing coronary mortality.⁹

Need for Research

Adverse effects in this category are unlikely to be discovered informally. In the first place, a discernible epidemic would not tend to arise — for example, if the drug is taken by 10 per cent of the population, and if it doubles the rate of the illness, the drug still accounts for only about 10 per cent of the cases. Furthermore, the experience of any single physician would generally be insufficient to discern, say, a doubling of the rate of the illness among users of the drug or, alternatively, a doubling of the usage rate of this drug among patients with the illness. Finally, even if the drug effect were suspected informally, confounding would remain a likely explanation in the absence of formal analysis of the experience.

Since drug-illness relations in this category would tend to escape detection by routine clinical observation, the particular illnesses that may be caused by a drug deserve special attention. Aside from epidemics of certain infectious diseases, annual attack rates of at least one in 200 are associated with essentially no serious illnesses but acute manifestations of cardiovascular disease — most notably, acute myocardial infarction and sudden coronary deaths — in certain high-risk populations. Thus, research needs on the illnesses of concern tend to be quite limited in this category.

Considerable information on the influence of some drugs on the course of coronary heart disease is already available. Numerous clinical trials involving over a dozen important drugs have been carried out.⁹⁻¹⁵ Beyond this experience, a large body of relevant data has been accumulated by the Boston Collaborative Drug Surveillance Program¹⁶: the histories of drug use in some 2000 patients with acute nonfatal myocardial infarction have been contrasted with histories of other patients.¹⁷⁻²⁰ No definite indications of drug cause have emerged. The data, however, are insufficient to exclude drug associations of the order of magnitude of, say, twofold, except for reasonably commonly used drugs. Moreover, in terms of the control of confounding factors, it is not feasible to explore the potential etiologic role of drugs used to treat predisposing illnesses or to treat coronary heart disease itself.

Strategy for Research

As an example of formal research in Category 4, one can examine the origin of the hypothesis that tolbutamide is conducive to fatal coronary heart disease.⁹ A clinical trial had been mounted with the primary aim of assessing the relative efficacies of alternative treatments for adult-onset diabetes. Among the complications potentially prevented by the drugs were myocardial infarction and sudden death. Quite unexpectedly, these complications occurred more commonly in the tolbutamide-treated group than in the placebo-using reference series. The difference was "statistically significant," and confounding was dealt with through randomization of treatment allocation, augmented by the control of certain factors in the analyses. Despite the experimental nature of the design, there has been substantial controversy about the validity of the comparison and, therefore, about the inference itself.^{21,22}

Experimental evaluation of the relation of coronary heart disease to drugs at large, although it is the most valid approach because treatments are randomized, requires separate randomized series for all the drugs of concern. Experimental evaluation of a newly marketed drug and drugs of special interest can be accomplished, though it should be noted that long-term clinical trials frequently cost millions of dollars.^{4,5} For the evaluation of the multitude of drugs already in clinical use, the experimental approach is obviously infeasible.

A nonexperimental cohort study is amenable to simultaneous evaluation of a multitude of drugs. As compared to the case-referent approach, the cohort approach requires the enrollment of much larger numbers of subjects and the follow-up study of those subjects for the recording of drug use and subsequent occurrence of the illness. Thus, follow-up studies tend to be relatively costly and time consuming, particularly if conducted prospectively.²³

The case-referent approach permits evaluation of the role, in a single study, of many drugs as the cause of a particular illness. The cost of such studies, when done individually, is frequently no more than a few thousand dollars and rarely more than tens of thousands of dollars. Though very efficient and permitting the enrollment of large numbers of cases, this approach has the potential for bias from several sources, particularly in the areas of subject selection and information gathering. When these problems are insurmountable, the case-referent approach is not applicable.

BOTH RATES IN THE INTERMEDIATE RANGE (CATEGORY 5, TABLE 1)

In this circumstance, the added risk associated with a drug is neither "high" nor "low," and the base-line risk of the illness is also in the intermediate range. An example is the apparent connection between the use of exogenous estrogens and the risk of endometrial cancer.²⁴

Need for Research

Adverse drug effects in this category are unlikely to be discovered informally, since the proportion of incident cases of the illness due to the drug is usually only a small fraction of the total cases, and no discernible epidemic occurs. Thus, even the exceedingly strong association between estrogens and endometrial cancer went undetected for over 20 years until formal case-referent studies directed to the evaluation of this specific relation were carried out.

As for illnesses of concern in Category 5, the incidence rates of the spectrum of serious illnesses that are potential candidates for drug induction reveal that all cancers, except for the rarest forms, qualify. Only a few additional illnesses meet these criteria. Among them are gallbladder disease, cataract and peptic ulcer. Substantial series of cases of these three diseases, as well as others in Category 5, have been accrued by the Boston Collaborative Drug Surveillance Program.²⁵⁻²⁷

Strategy for Research

An example of formally discovered relations in Category 5 is the association between oral contraceptives and gallbladder disease.²⁵ A series of 212 premeno-

pausal women who had undergone gallbladder operations were collected by the Boston Collaborative Drug Surveillance Program during a hospital survey. They were compared to 842 women hospitalized for other conditions presumed to be unrelated to oral-contraceptive use. Analysis of the data yielded the estimate that users of oral contraceptives were twice as likely as nonusers to undergo gallbladder operations.

For the discovery of drug-illness relations of this kind, the case-referent approach, once again, has a substantial feasibility advantage in the study of drugs already on the market. Follow-up studies would entail the monitoring of huge numbers of patients for many years to evaluate the many drugs currently marketed in relation to the illnesses of importance in this category.

For newly marketed drugs, registry and follow-up observation of early users are indicated for prompt identification of drug-illness relations. The interpretation of data, however, may be more complex than that involving rare diseases. The quantitation of the relation of a drug to an illness that occurs reasonably often in the absence of drug cause generally requires a carefully drawn reference or comparison group not exposed to the drug. This matter may be managed if a number of follow-up series are being monitored simultaneously — i.e., one for each of a number of newly marketed drugs. Under such conditions, each may act as a reference series for the other.

DISCUSSION

This analysis of potential undiscovered drug-illness relations, organized according to the magnitude of the drug effect and the base-line risk of the illness of concern, points to the following research policy and strategy:

Unrecognized effects of established marketed drugs in causing rare but serious illness, such as aplastic anemia, can be discovered most efficiently by the use of case-referent studies. Systematic study of selected illnesses of this kind may be called for, so far as there is reason to suspect that such side effects may have escaped clinical detection.

Currently marketed drugs may also be responsible for increased risk of illnesses with an intermediate base-line rate of occurrence. If the effect is appreciable, it is subject to discovery nonexperimentally, again, most efficiently, by the use of case-referent studies. Since these adverse effects may be important and not readily amenable to clinical discovery, systematic study of various cancers and perhaps some other conditions of this type is called for.

Concerning the drug cause of illnesses with high base-line risks, information on acute manifestations of coronary heart disease — essentially the only important illnesses in this category — has already been accrued from various clinical trials and through the experience of the Boston Collaborative

Drug Surveillance Program. Additional ad hoc trials may be indicated. However, the high cost of such studies demands careful attention to priorities for the particular drugs that could be most usefully studied.

Newly marketed drugs should be routinely and systematically monitored for toxicity through compulsory registration and follow-up study of the earliest users.

Although the case-referent type of study has been widely acknowledged as a legitimate research tool,^{28,29} and appears to be the approach of choice for the discovery of most unsuspected serious drug-illness relations, it is important to note that many scientists are highly sceptical of the validity of the inferences resulting from such studies.^{30,31} This discordance of views will have to be faced in the establishment of research policy in the area of drug-induced illness.

Finally, most important drug-illness relations should be readily and inexpensively discoverable without the need for independent special studies if a complete and accurate long-term record of drugs taken by a large defined population were collected, and if a computerized pharmacy were used, together with a means of linking data so collected to hospital-discharge diagnoses that could be validated. Comprehensive health plans could be appropriate settings for the initiation of such a program.

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