CHALLENGES IN DRUG EVALUATION IN MAN

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After centuries of clinical evaluation of drugs that proceeded primarily by trial-and-error and serendipity, the field of clinical pharmacology has begun to develop, during the last two decades, a foundation of principles and techniques that will ultimately provide a scientific basis to drug development and use. Even a cursory glance at a recent attempt to summarize "the state of the art" (1) will suffice to show the interested reader how substantial this foundation already is. What this essay will attempt is a brief description of some important areas of drug evaluation that deserve special attention and emphasis.

COMPARATIVE EFFICACY AND INDIVIDUAL "TAILORING" OF DRUGS

One of the hallmarks of the revolution in clinical pharmacology is its emphasis on comparative efficacy, and on the reliability and precision with which such comparisons can be made. It is a trivial matter, in almost all instances, to say that a drug has therapeutic efficacy. What is desired, rather, is to know how much better (or worse) the drug is than nothing at all, or a placebo, or a standard remedy.

There are several ways of comparing drugs. One common technique is to pit the "standard" dose of one against the "standard" dose of another. While such an experiment is not devoid of interest, it is less informative, both in terms of efficacy and toxicity, than a trial comparing two or more dose levels of each drug. The latter type of experiment, if a dose-response relationship can be successfully demonstrated, is much less likely to mislead the investigator and the reader than is a comparison of single, arbitrarily chosen dose levels. Unfortunately, time, availability of experimental subjects, and ethical considerations usually force a compromise between the multiple point assay, with reasonable numbers of observations per point, and the more limited dose exploration that is realistically possible.

With drugs that are to be taken repeatedly in the management of a more or less chronic disease or symptom, an increasingly popular method of dosing in clinical trials is to select a starting level of dose, but to raise or lower the dose, within limits, depending on whether the desired effect is lacking or

suboptimal, or side effects supervene. This technique, while not permitting a standard dose-response type of potency assay, at least resembles the kind of bioassay that is often indulged in by clinicians in the practice of medicine, and has the advantage of compensating for such inter-individual sources of variation as the inborn (or acquired) differences in enzymatic capacity, which can at times produce dramatically different plasma half-life values in both animals and man.

This flexibilized dosage approach is in a sense a "tailoring" of drug to patient need. But there is a broader sense in which tailoring is required if the precision of our trials and of our therapeutic endeavors is to be sharpened. I refer to the many nondrug variables that may affect response to a drug. Let us take, for example, a common situation. A trial is completed and reveals that treatment A relieves pain satisfactorily in 80 per cent of the patients, whereas treatment B relieves only 20 per cent. One is usually not in a position to know whether the 20 per cent of patients relieved by treatment B are in fact also capable of being relieved by treatment A, or whether some or all of them constitute a separate group of patients who are best treated in fact with treatment B. Clearly, if there are B-responders who are not responsive to A, a proper and prompt selection between treatments A and B will increase the ability of the physician to relieve pain. In the absence, however, of knowing how to predict who is an A responder and who is a B responder, or whether indeed there are any specific B-responders, the clinician will administer treatment A first to all patients, since it is statistically the most likely to relieve pain.

When real and consistent differences between treatments exist, one would like to know the reason for the differential response. Is it the nature of the disease, the age or sex of the patient, or what? In animals, we know that strain, age, sex, temperature, time of day, size of container, number of "neighbor" animals, etc., can profoundly affect responses to drugs. The contribution of the underlying personality of the patient (2) and of his reasons for participation in an experiment (3) have been well demonstrated. Feinstein has nicely documented the importance of both anamnestic data and histologic classification in the prognosis of certain types of cancer, having previously shown the variable prognosis associated with different types of acute rheumatic fever (4).

Earlier disagreements as to the role of antibiotics in the management of primary atypical pneumonia have been more or less resolved with the accumulation of information allowing us to separate out the one type of such pneumonia caused by Mycoplasma organisms. This latter type responds to certain broad spectrum antibiotics, whereas other types apparently do not.

It is obvious that such entities as "coronary artery disease" or "hypertension" are heterogeneous designations, and that within each group, as within such groups as "schizophrenia," "depression," etc., are to be found sub-groups that will respond differentially to drugs. Recent experience with toxic reactions caused by drugs given in combination, or by interactions be-

tween ingested food stuffs and drugs again attest to variables that may affect the response to a given drug. Different observers may rate the response to treatments differently, depending on the criteria they are using for estimating drug response (5).

A more scientific approach to this field will require greater attention to the possibility of such nondrug variables contributing significantly to the variance in an experiment. While routine attention to certain patient characteristics such as age and sex may help, it is also likely that many important variables will not be apparent as such to the investigator, and it seems reasonable to search for correlations empirically by the use of computer, feeding into the machine patient characteristics of all sorts, and relating these to drug response. Such an attempt has already been made in the area of psychiatric illness, with certain constellations of symptoms apparently predisposing to differential response to drugs (6). "Fishing" expeditions of this sort will often come up with false leads, but the attempt to define important correlations seems worthwhile.

Comparative Drug Toxicity; Toxicity Monitoring; Early Detection of New Forms of Toxicity

The status of our methodology for evaluating the therapeutic effects of drugs in quantitative fashion is reasonably satisfactory. By contrast, our methods for quantifying toxicity are much more primitive. In trials the investigator is usually aware of what therapeutic effects he is searching for, whereas untoward effects are both more variable and less predictable. Compounding the difficulty is the fact that certain side effects, including serious ones, may occur so infrequently that average sized comparative trials will miss their occurrence. In addition, startling new forms of toxicity can be created by interactions between drugs, or between drugs and ingested food stuffs, or may appear after the offending drug has actually been stopped (7). Furthermore, most toxicity is not in the form of unique symtomatology or signs, but rather in the nature of subjective or objective complaints that may also be observed in the absence of medication. Thus when a drug leads to toxicity that is commonly seen in absence of the drug (such as gastrointestinal bleeding or thromboembolism), and the drug causes such toxicity rarely, one may need careful epidemiologic studies to delineate a cause-and-effect relationship. It should be remembered that even the dramatic "seal babies" that occurred following ingestion of thalidomide by pregnant women had been known to occur before thalidomide and have been seen since withdrawal of thalidomide from the market.

There is considerable interest in reducing the lag time for realizing that an unpredicted type of side effect is caused by a drug. Finney has suggested the scrutiny of patient records, in a search for such previously unsuspected toxicity (8). Some hospital-based groups have routinely monitored drug administrations in a hospital with the same purpose in mind. International studies are now under way under the auspices of the World Health Organiza-

tion, attempting to collate reports of untoward drug effects, as well as examine temporal and geographical patterns of response, with the intent of sharing information and alerting the world medical community to the possibilities of drug mischief at an earlier date than has been possible in the past.

There would seem to be a place for improved post-marketing surveillance of new drugs. It might be possible, if a systematic attempt were made to record both the therapeutic performance and the side effects seen during the first year or two after a drug's introduction on the market, to assemble important new information about the drug's efficacy and safety. Systematic monitoring has usually not been applied in the past, and any techniques utilized would have to have enough rigor and completeness of response (even in a sample of patients) to make the exercise something other than a futile gesture.

The Use of the Computer in Guiding Therapeutics

The information explosion in pharmacology has made the practice of medicine increasingly difficult. In a sense we have been too clever for our own good in uncovering new drugs and new applications for them. It is rapidly becoming impossible for any physician to keep track of all the important drugs, both new and old, that he should use in his clinical practice. Providing up-to-date information on the indications and contraindications of these drugs, and their possible interactions with other drugs or non-drug variables, constitutes an exciting challenge. Weed (9) has suggested that a solution to this problem may come via the intelligent use of computers. If accurate and updated programs were available, physicians could quickly get reliable information in the hospital or office as to what drugs are available and recommended for a given disease state, what toxicity to be on the lookout for, and what other important points the physician should keep in mind. Such programs would require, for optimal performance, reasonably precise information as to the therapeutic batting average and incidence of toxicity associated with a given drug, and with other drugs available for treating the same disease or symptom. It seems inevitable that such computer programs will evolve, and it would behoove those expert in the field of clinical pharmacology and therapeutics to see that the programs devised are of first-rate quality.

Pharmacokinetics; Modification of Dosage Regimen

The evolution in regard to biopharmaceutics in the past decade has focussed the attention of the scientific community on our presently outmoded *in vitro* criteria for assessing the ability of a drug to perform well clinically. Evidence that "certified" batches of chloramphenicol performed poorly in volunteer blood level studies (10) has dramatized the need for considering what sorts of data will be required for the marketing of generic versions of standard drugs. It would seem inappropriate to demand new clinical trial

data on every proposed generic preparation, but it also seems unwise to rely completely on *in vitro* data. Some sort of physiological availability studies will probably be used as a compromise, with the present focus being on blood level measurements. Such measurements, either in animal or man, will at the very least give some information as to the speed, completeness, and predictability with which drugs are absorbed into the blood stream. For many drugs, however, we do not have definitive information as to what blood level of drug is required for therapeutic effect, or whether continuous blood levels are needed. History has taught us that drugs can vary tremendously in regard to the correlation of therapeutic effects and blood levels (11). With some chemotherapeutic agents, for example, adequate blood levels must be maintained in order to produce a therapeutic response. With others, days may elapse between administration of drug, with long periods when the blood and body tissues are drug-free, with no loss of therapeutic activity. If wise and equitable decisions are to be made in regard to the monitoring of generic preparations, it would seem important to accumulate data on such correlations.

Closely linked with the above consideration is the possibility that variations in dosage regimen may be highly important in determining the therapeutic impact of the drug. It can be shown for a drug like chlorothiazide, for example, that the same amount of daily drug split up into small aliquots given repeatedly during the day is more effective in mobilizing fluid and salt from the body than if the total dose is once a day (12). In the field of cancer chemotherapy, there is considerable interest at present in experimenting with continuous versus discontinuous regimens of dosage, in an attempt to reduce toxicity, improve efficacy, or both.

Effect of Drugs on the Gastrointestinal Mucosa

It is becoming increasingly apparent that drugs, whether taken acutely or chronically, may affect intestinal structure and function. The sprue-like syndrome seen after neomycin (13) or the instances of malabsorption of nutrients after antituberculous or anticonvulsant therapy (14) are examples of this phenomenon. It is remarkable that for so many years the administration of drugs via the gastrointestinal tract has not awakened the minds of the scientific community to the possibility that such drugs, and perhaps especially those taken repeatedly, might frequently affect the structure and function of the gastrointestinal tract. While there has been interest in fairly dramatic types of gut toxicity, such as the bleeding from alcohol or aspirin, or the intestinal ulcers resulting from enteric-coated potassium tablets, more subtle effects on mucosal structure and function have generally been disregarded. It seems highly probable that many drugs that bathe the gastric and intestinal mucosa, or that pass through mucosal cells on their way into the body tissues, will cause detectable anatomic or physiologic change by virtue of their contact with these gut cells. Physiologic and anatomic exploration of this problem in animals and man should yield important scientific pay-off.

Drug Selection and Marketing

Certain aspects of the selection of drugs for clinical trial and their introduction into the marketplace seem to deserve the attention of the scientific community, in the hope of coming up with rational guidelines. Take, for example, the problem of how many preclinical toxicity tests are required before a drug is used in man. At present, the approach is primarily an arbitrary one, based on what has seemed to work in the past. Yet within this framework of arbitrariness, one can question the exact duration of time required for toxicity tests, the numbers of animals or the species chosen, the types of laboratory tests required, etc. How many toxicity tests are enough would seem to be a question that must be answered in probabilistic cost-benefit terms, and that therefore the empirical correlation of data from animals and man would help to decide the interesting and important questions posed above. The ultimate decisions must be made by balancing the dangers that come from inadequate testing against the losses to the public arising from requirements that are excessively rigid, expensive, and time consuming.

The same types of problems apply to the performance of "Phase I" or "Phase II" trials. Are pharmacokinetic and biotransformation studies usually desirable in Phase I? How many subjects should be studied in this phase? What types of subjects? What subjective and objective variables should be monitored? How should the starting dose be chosen? By what increments should this dose be raised in the absence of alarming side effects? At what intervals should the dose be increased?

In regard to Phase II and Phase III trials, how much data are required for moving from one phase to another, or for moving from Phase III to marketing? The National Academy of Sciences has expressed an interest in helping to formulate guidelines for the Food and Drug Administration in regard to such questions, and it would seem an important problem to which to address ourselves. Final judgments will probably be based on a combination of empiric experience and theoretical considerations.

Ethical Problems

The current atmosphere pervading scientific investigation in the United States, and the requirements of the Food and Drug Administration and the National Institutes of Health, emphasize the importance of obtaining informed consent from human subjects in an experiment. Unfortunately, the focus thus far has been on form rather than substance. Investigators of new drugs, for example, are expected to explain in considerable detail, to their experimental subjects, the purposes and plan of the experiment. Yet it is clear that excessive detail may interfere with the communication of crucial information to the subject (15). There has thus far been a minimum of attention to techniques for ascertaining whether in fact subjects have adequately comprehended the problem at hand.

There has also been little study of the impact of written consent (as opposed to traditional verbal or implied consent in ordinary patient-doctor or subject-investigator relationships) on these relationships as well as on the experiments themselves. There has been a similar disregard for the impact of complete candor as to the details and purpose of an experiment on the response of subjects to experimental variables, including the placebo.

In drug studies involving psychiatrically ill patients or children, there are additional ethical questions (16). Under some circumstances, these subjects may be incapable of giving consent on their own, and to rule them out as experimental subjects may deprive them of certain important drugs. In such instances, it would seem ethical to involve third party permission. On the other hand, in as many situations the additional consent of the patient, adult or pediatric, should probably be obtained. Many psychiatrically ill patients and many children are capable of comprehending the nature of an experiment and its potential benefits and risks, and it is questionable whether such subjects can be ethically studied if they strongly object to an experiment. This problem is particularly worrisome in psychotropic drug studies, since in the field of psychiatry conditions are treated where the patient, his physician, his family, and society at large may disagree considerably on even the presence of mental illness, let alone the desirability of its modification by drugs.

A final area of ethical difficulty is posed by the use of challenge doses of drug to elucidate cause-and-effect relationships in drug toxicity. In some patients, the readministration of a dose of drug suspected to have caused a drug reaction will result in a recrudescence of the symptoms or signs constituting the reaction. Such successful challenges are often extremely convincing. Nevertheless, since they pose hazards to the subject, it would seem desirable to limit their use and for scientific investigators to delineate the conditions under which challenge may be tried. It is suggested that the following conditions may justify such challenge:

(*a*) The lack of an *in vitro* test for the drug reaction in question.

(*b*) The present or future need of the patient for the particular drug in question or for chemically related drugs.

(*c*) A type of toxic effect that is neither productive of permanent damage nor life threatening.

(*d*) The availability of facilities for proper management of any untoward events that occur.

(*e*) A full exposition of the problem and risks involved to the patient in question, with informed consent.

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