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Editorial

Patient-Oriented Pharmaceutical Research: Focus on the Individual

One view of the pharmaceutical sciences, broadly defined, is that they are concerned with the development of a knowledge base that leads to a) the discovery of new drugs and the development of appropriate dosage forms for them, and b) the optimization of pharmacotherapy for individual patients. The enormous changes in health care and in the pharmaceutical industry that have occurred in recent years are causing an increased emphasis on outcomes-oriented optimization of pharmacotherapy and the consequently anticipated economic benefits to health care insurers and providers such as HMOs (i.e., fewer hospitalization days and unscheduled physician visits, and a reduced need for medications to treat adverse reactions and other consequences of suboptimal pharmacotherapy).

Optimization of pharmacotherapy for individual patients requires proper diagnosis, an effective treatment plan including the selection of the most appropriate medicinal agent(s) for pharmacotherapy, and design of the proper drug dosing regimen. The knowledge base and tools of the pharmaceutical sciences are particularly suitable to address the issues of determining and instituting the most appropriate dosing regimen for individual patients. This is a matter of pronounced social and economic importance for, as we have learned only recently, there are very large differences among individuals in how they dispose of and react to a particular medication, i.e. in pharmacokinetics and pharmacodynamics.

Progress in the sciences is usually limited by our ability to measure relevant processes or characteristics. Pharmacokinetics "took off" when specific and sensitive analytical methods to measure drug and drug metabolite concentrations in biological fluids and tissues became available. Only then did we discover that some drugs are not fully absorbed, that the pharmaceutical dosage form can affect bioavailability, that some drugs are subject to presystemic biotransformation, that drug disposition can be subject to genetic and environmental influences, and that the pharmacokinetics of a drug can be saturable and/or time dependent. An awareness of these realities led to an appreciation of pharmacokinetic individuality and an awareness of the large interindividual differences in the pharmacokinetics of many drugs. The practice of clinical pharmacokinetics evolved as a consequence of this awareness.

In retrospect, the development of clinical pharmacokinetics services in hospitals may have been premature and it is not surprising that the efficacy and cost-effectiveness of this service has been questioned. It was based, in practice at least, on the naive assumption that pharmacokinetic variability is the major, if not the sole cause of interindividual differences in the pharmacologic response to a given drug dosage regimen. The "therapeutic blood level", i.e. the usual range of drug concentrations in plasma associated with relatively safe and effective therapy, was often viewed as a hard number even though most such numbers were based on very soft and limited clinical evidence. Many physicians (and pharmaceutical companies!) adopted a similarly rigid attitude with respect to drug dosage, even disregarding the substantial gender difference of body weight in their posology. Failure to appreciate that the proper dosage of morphine differs by more than two orders of magnitude between individuals has been largely responsible for the inadequate management of severe pain that became a national scandal. Many other such examples can be cited. Almost all are ultimately due to a failure to appreciate that in the design of individually optimized drug dosage regimens one must take account not only of pharmacokinetic but also of pharmacodynamic individuality.

The development of requisite tools and skills to measure pharmacologic effects was driven largely by regulatory requirements for demonstrating the therapeutic efficacy of new drugs. It was facilitated greatly by advances in pharmacodynamic modeling; modelers need and demand good data and they recognize poor quality data. Pharmacometrics will be advanced even more forcefully by the insistence of HMOs on rigorous demonstration of efficacy and cost-effectiveness as a prerequisite for admitting new drug products to their formularies. In any event, even the relatively limited information presently available shows that the magnitude of pharmacodynamic variability is similar to and often exceeds that of pharmacokinetic variability. No wonder that clinical pharmacokinetic services focused largely on monitoring and adjusting drug-in-plasma concentrations to a fairly arbitrary range have not been very effective! There are exceptions, of course, particularly in cancer chemotherapy, where acute toxicity is usually dose-limiting and plasma concentration monitoring can prevent undue toxicity in slow metabolizers and subtherapeutic drug concentrations in relatively fast metabolizers of a drug. Renal failure and organ transplantation are other cases where drug concentration monitoring is often essential but here too the efficacy of this service is frequently limited by uncertainties about disease-associated changes in drug concentration-effect relationships.

The third essential component of a relatively safe and effective drug dosage regimen has been largely neglected by pharmaceutical scientists because until recently it was difficult to measure and therefore difficult to deal with. It is medication adherence, often called compliance in the past when physicians acted in a more paternalistic context. The recent availability of various types of electronic medication use monitors has revealed all sorts of interesting and important aspects of medication nonadherence; it is frequent, occurs in many different patterns and is apparently due to

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many different causes. It can have a profound influence on health care outcomes and on the results and interpretation of clinical trials.

Pharmacokinetics, pharmacodynamics and medication adherence are the inseparable components of effective, individually optimized pharmacotherapy. In turn, the focus of pharmaceutical research, originally mainly chemical and physicochemical, had to expand over the years to encompass the biological and must now also include certain aspects of the behavioral sciences. Might it be that future issues of *Pharmaceutical Research* will contain some reports of behavioral research related to medication adherence?

Perhaps the greatest unmet need is that of identifying useful covariates (predictors) of pharmacodynamic individuality. Many such covariates are known with respect to pharmacokinetics: renal function, age, protein binding, liver disease, thyroid disease, smoking, diet, and interactions with other drugs among them. We are as yet unable to establish a similar checklist to help us identify potential covariates of pharmacodynamic parameters. Much of the checklist for pharmacokinetics was derived from studies in animals. Similar preclinical studies will be useful in pharmacodynamics, as has already been shown. The ultimate aim of all these efforts should be to provide guidelines (some have called them user's manuals or software) to physicians to help them determine the most appropriate drug dosage regimens for individual patients without fumbling and undue delay.

It is important for pharmaceutical scientists to appreciate that the triad of pharmacokinetics, pharmacodynamics and medication adherence must be addressed not only in terms of central tendencies but with respect to individual differences and their determinants. For practical and economic reasons a need for routine monitoring of drug concentrations in plasma would be an undesirable and frequently unacceptable feature of a medication. Other than for certain drugs used to prevent serious and episodic morbidities such as epileptic seizures and organ rejections, the inconvenience and cost of pharmacokinetic monitoring rule out its routine use, particularly in outpatients. If the relevant pharmacologic effects of a drug are readily quantifiable by practitioners and occur without significant delay, titration of drug dosage is feasible and can be efficient in both institutionalized and outpatients. Otherwise, for example in the case of many psychotherapeutic agents and of course in the treatment of episodic or slowly developing diseases without suitable surrogate markers, individual optimization of the drug dosage regimen can be slow, costly, and imperfect. Medication nonadherence can invalidate all other aspects of pharmacotherapy and can have serious public health consequences, such as in the treatment of tuberculosis. Pharmaceutical research will have to focus on the determinants and covariates of pharmacokinetic and pharmacodynamic variability with the aim of developing algorithms to predict the dose-concentration and concentration-effect relationships of a particular drug in individual patients based on their demographic and other relevant characteristics, if at all possible. Equally necessary is a search for predictors of medication adherence and of course for methods to enhance it.

Unfortunately, none of these efforts can be generic; the issues are largely drug- and disease-specific. Addressing them will take time and cost money, neither of which is in unlimited supply. How far do we go, then? HMOs will be willing and able to support this effort when it promises to reduce costs, particularly that of the "big-ticket" item, days of hospitalization. The National Institutes of Health can be expected to respond to opportunities for the treatment of the politically most visible diseases such as AIDS and cancer. Pharmaceutical industry will probably be most attracted to the pharmacotherapy of diseases affecting large populations such as cardiovascular and (when good drugs become available) Alzheimer's. Regardless of the setting and the circumstances, there will be much to do for pharmaceutical scientists committed to achieving the best possible outcomes in the use of medications. Focus on the patient as an individual is not only the duty of physicians and other health care professionals but is also becoming an increasingly important obligation of pharmaceutical scientists.

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