

Individualization of drug therapy: an historical perspective

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Although therapeutic drug monitoring, pharmacokinetics, and pharmacogenetics/ pharmacogenomics are conventionally considered in isolation, when applied to patient care, they are really three chapters in a continuing story that has as its theme the optimization of pharmacotherapy. This has been variously referred to as "rational drug therapy", "individualization of drug therapy", and "personalized medicine". However, the goal of improved drug therapy has been the same.

Therapeutic Drug Monitoring

The origins of therapeutic drug monitoring can be traced back to 1927 when Otto Wuth[1] described the monitoring of serum bromide concentrations as a valuable adjunct in using this drug as an anticonvulsant or sedative. Particularly noteworthy is that Wuth outlined the rationale for this approach in much the way that would be done by contemporary clinical pharmacologists.

The advent of WW II brought military operations in tropical areas that focused attention on the need to treat, or better yet prevent, malaria in combat troops. A Committee on Medical Research was formed in the United States.[2] The Committee sponsored Brodie and Udenfriend to develop of a rapid and simplified spectrophotofluorometric method for measuring serum levels of quinine.[3] This method also was found to be applicable to the measurement of serum levels of its stereoisomer, quinidine. However, the early loss of the usual sources of quinine supply compelled both Germany and the Allies to seek alternative therapies. Quinacrine (Atabrine) had been evaluated as a quinine alternative by the Germans but had been discarded because it appeared

to lack the rapid efficacy required for optimal prophylactic use. Fortunately, when quinacrine was later evaluated by Shannon and colleagues,[2] they had the advantage of using a spectrophotofluorometric serum level assay that Brodie and Udenfriend[4] developed. Aided by this method, Shannon and his team[2] determined that a quinacrine loading dose was needed in order to rapidly achieve the high plasma quinacrine levels that were required for rapid efficacy.

This wartime experience prompted an increased interest in measuring drug concentrations in patient serum or plasma. In 1951, Mark and colleagues that included Brodie,[5] described a spectrophotometric method for measuring plasma procainamide concentrations and other spectrophotometric or colorimetric methods were developed for a number of drugs. Unfortunately many of these methods were too cumbersome and time consuming for widespread routine clinical application, so the development of laboratories dedicated to therapeutic drug monitoring of a variety of drugs awaited the development in the late 1960's and early 1970's of drug assays that utilized radioimmunoassay, gas chromatography, and high-performance liquid chromatography.[6] The specialized equipment and expertise required for these newer assays was not generally found in clinical chemistry laboratories, so therapeutic drug monitoring was in many cases carried out as part of clinical pharmacology programs that had a vested interest in interpreting the results and in combining them with pharmacokinetic analysis to individualize drug therapy in patients.

Once the clinical utility and revenue potential of therapeutic drug monitor-

ing had been demonstrated, companies began to develop automated systems that enabled routine technicians to perform these assays without special training. One popular automated technique was based on fluorescence polarization immunoassay.[7] In addition, the College of American Pathologists initiated an interlaboratory quality control program to ensure that reliable results were being obtained.[8] The result of these developments was that provision of assays for therapeutic drugs migrated from dedicated clinical pharmacology laboratories to become just one of the panoply of tests offered by clinical chemistry laboratories. Despite the financial benefits that may have accrued from this consolidation, the individuals supervising these assays no longer had the same interest as clinical pharmacologists in assisting clinicians in interpreting and optimally utilizing the assay results. In addition, pharmaceutical industry marketing departments preferred to claim that a one-size-fits-all dose of their drugs obviated the need for the extra time and expense required for therapeutic drug monitoring. Finally, many drugs for which therapeutic drug monitoring had been advocated were no longer used as commonly. So the net result of these developments was that therapeutic drug monitoring decreased in prominence as an aid to individualizing drug therapy.

Clinical Pharmacokinetics

On the basis of two articles published in 1937, Teorell has been regarded as the founder of pharmacokinetics.[9] During the 1940s, it was realized that loading doses played an important role in the development of antimalarial therapy and

Gaddum elucidated the plateau principle that characterizes how the time course of attainment and eventual magnitude of steady state drug concentrations depend on the rates of drug dosing and elimination.[10] However, it was the availability of therapeutic drug monitoring that first made pharmacokinetics a practical adjunct to the care of individual patients. One important result was that the excessive digoxin loading doses that were previously recommended were reduced so as to be commensurate with expected steady state plasma levels. The fact that most drugs were eliminated by apparent first-order kinetics made it relatively easy to use steady-state drug concentrations to guide subsequent dose adjustments.

However, pharmacokinetics probably made its most clinically significant contribution when used to guide drug dosage in patients with impaired renal function. In 1974, Jelliffe[11] developed a simple nomogram that even innumerate clinicians could use to estimate proper digoxin dosage based on a patient's weight and creatinine clearance. At about the same time, Dettli[12] introduced a more comprehensive method for estimating appropriate drug doses for patients with impaired renal function. The method was based on drug clearance in subjects with normal renal function and the percentage

of this clearance that represented renal elimination of unmetabolized drug. Its most critical assumption was that non-renal clearance remain unaltered in the face of declining renal function. This assumption has been found to be invalid for a number of drugs and for several different elimination pathways. However, there is a lack of data to indicate the level of impaired renal function at which the assumption breaks down. The importance of providing the necessary information for these dose adjustments to be made is emphasized by the US FDA's draft guidance for the conduct of studies in patients with impaired renal function.[13]

The first hospital laboratory that was dedicated to the combination of therapeutic drug monitoring with pharmacokinetics probably was developed by Sjöqvist and his colleagues at the Huddinge Hospital. Particular attention was focused on tricyclic antidepressant drugs because patients showed marked differences in their response to these drugs, accurate analytical methods were available, and there was a general need for pharmacokinetic approaches for treating patients with psychiatric diseases.[14] Studies by these investigators elucidated the pharmacokinetics of nortriptyline and demonstrated the need for therapeutic drug monitoring by showing that the curve

relating steady state levels of this drug to antidepressant response had an inverted u-shape, with optimal efficacy being observed with plasma levels between 50 and 109 ng/mL. In additional studies, they found that monozygotic, but not dizygotic twins had remarkably similar steady state nortriptyline plasma levels. This led them to conclude that, when the effects of concurrent drug administration could be excluded, most of the interindividual variability in these levels was genetically determined. These findings paved the way for pioneering investigations that helped

usher in our current pharmacogenetic/pharmacogenomic era.

The Pharmacogenetic/Pharmacogenomic Era

The use of primaquine in malaria program during World War II also focused attention on genetic variants that predispose to adverse drug reactions. A hemolytic reaction that occurred in susceptible individuals treated with prolonged high doses of primaquine was associated with a variant gene located on the X-chromosome. In 1956, this variant was shown by Carson et al.[15] to lead to a deficiency in glucose-6-phosphate dehydrogenase. Subsequently, other pharmacogenetic variants were shown to affect the rate of drug metabolism. Early examples of these were the identification by Price Evans et al.[16] of rapid and slow acetylators of isoniazid in 1960 and by Eichelbaum et al.[17] of rapid and slow metabolizers of sparteine, now known to be caused by polymorphisms of NAT and CYP2D6, respectively. This latter polymorphism has been extensively studied and has been reported to affect the rate of metabolism of approximately 25% of currently marketed drugs,[18] including the antidepressant drugs studied by Sjöqvist et al.[14] Currently there is accumulating evidence that important pharmacogenetic/pharmacogenomic differences in some cases extend to transporter function and to pharmacodynamic response.

In recognition of the increasing significance of pharmacogenetic/ pharmacogenomic factors, a Genomics Group has been formed in the Office of Clinical Pharmacology at the US FDA Center for Drug Evaluation and Research.[19] The Genomics Group has played a central role in reviewing emerging pharmacogenetic/ pharmacogenomic information and in screening this information for suitable incorporation in drug labels. In addition to this highly visible activity, the Genomics Group also provides important guidance to sponsors during the drug development and approval process. The NIH sponsored Pharmacogenomics Research Network has also formed a Clinical Pharma-

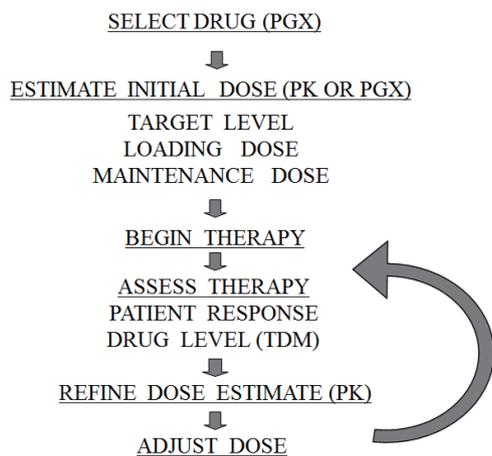


Figure 1. Drug prescribing flow chart showing the potential application of pharmacogenetics/pharmacogenomics (PGX), pharmacokinetics (PK), and therapeutic drug monitoring (TDM) at each step of the prescribing process.

cogenetics Implementation Consortium that provides peer-reviewed guidance for pharmacogenetics-based drug selection and dosing.[20] This guidance is based on the availability of reliable genetic testing and a review of the evidence linking genetic variations to important drug-related phenotypes.

Clinical application of pharmacogenetic/pharmacogenomic testing has so far been largely limited to single-gene testing in conjunction with a specific drug. For example, CYP2D6 genotype testing may be performed for patients about to be started on a course of tamoxifen therapy. However, "preemptive" programs are in progress that entail simultaneous genotyping to prospectively identify a number of important drug-gene interactions.[21] This information can then be incorporated in a patient's electronic medical record to provide subsequent guidance as to drug selection and dosing.

Clinical Application

The drug prescribing flow chart shown in Figure 1 illustrates how pharmacogenetic/pharmacogenomic, pharmacokinetic, and therapeutic drug monitoring information can be used in concert to optimize drug selection and dosing. Of course, patient response should be the ultimate indicator of therapeutic success or failure and this is where clinical judgment is essential. The technical challenges for providing this information for routine clinical implementation have either been met or are being rapidly overcome. So at present, the greatest obstacle to their utilization is probably educational rather than technical.

To better equip physicians to prescribe the right drug in the right dose for the right patient, Sjöqvist[22] advocates a radical change in pharmacology education and points out that medical school teaching in this discipline is all too often provided by faculty that have lost contact with both drug development and pharmacotherapy. In addition, appropriate continuing education often is lacking at the level of senior medical students, house staff, and practicing physicians. With re-

spect to the latter, the American College of Physicians did include a chapter and examination questions that focused on clinical pharmacokinetics and the use of therapeutic drug monitoring in the 1982 edition of its Medical Knowledge Self Assessment Program.[23] However, even this modest effort at physician education was continued for only a few subsequent editions of the program. Education in the proper use of pharmacogenetic/pharmacogenomic testing poses an even greater challenge although it is urgently needed. Resolution of these challenges probably will best be accomplished through a team approach that includes individuals with varying areas of expertise and responsibility, and it is encouraging that this strategy is being employed successfully at the Indiana Institute of Personalized Medicine.[24] Hopefully, the dosing guidance provided by these teams will also be based on pharmacokinetic calculations and, where appropriate, recommendations for therapeutic drug monitoring.

Conflict of Interest

Nothing to declare

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