Commentary: Therapeutic Drug Monitoring in the 1990s
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Clinical Pharmacokinetics

It has been clearly established that use of clinical pharmacokinetics to predict drug concentrations and to optimize dosages results in better and more cost-effective health care through individualizing a patient's therapeutic regimen. Clinical pharmacokinetics must be viewed from several perspectives. Therapeutic drug monitoring (TDM) has resulted in the development of a new professionalism within the pharmacy. Today, many pharmacists practice clinical pharmacy with a subspecialty in pharmacokinetics. These individuals, ordinarily holding a Doctor of Pharmacy (Pharm. D.) degree, have established clinical pharmacokinetics consulting services in some hospitals. They are well trained and competent to perform these consulting services. Unfortunately, because of the economics of the times, they and their clinical pharmacokinetics consulting services are considered by many hospital administrators to be a luxury rather than a necessity. Therefore, clinical pharmacokinetic services, except for those located in certain teaching hospitals, are not thriving nowadays in the United States. Most hospitals rely upon their own physicians, pathologists, and (or) clinical chemists to provide the interpretive and kinetic support necessary for individualizing drug therapy.

The hard reality is that few medical institutions are willing to provide the necessary economic support essential to ensure the success of clinical pharmacokinetics consulting services.

It is easy to understand why this problem exists. Careful workup of a patient in an intensive-care unit, for example, requires a minimum of 15 to 30 min of the pharmacist's time. The pharmacist must then spend an additional 20 to 30 min summarizing the clinical data, entering appropriate data into a computer program, and generating an appropriate interpretive report, along with dosage recommendations. The interpretive report then has to be delivered to the floor, and the attending physician or house officer must be contacted by the Pharm. D., either by phone or in person, with his or her recommendations. Thus, the average initial consultation on a patient on a clinical pharmacokinetics service requires 45 to 60 min, depending on the complexity of the case. The case must be followed daily. Repeat consultations usually require 15–30 min. If the clinical pharmacist has other administrative duties as well, no more than four or five consultations can ordinarily be performed in a working day. Thus we find the Pharm. D. and clinical pharmacokinetics consultation services used most in intensive-care units or associated with specialty services (e.g., infectious disease, cardiology) rather than on the general hospital floors.

If we assume that the average Pharm. D. is self-supporting and generates his own salary of, say, $50,000 per year plus an additional $75,000 per year in operating expenses to support his service, he would have to generate a billable income in real dollars of approximately $500 per day during a five-day work-week. The actual cost effectiveness of a clinical consultation service is achieved through better patient care. The hospital saves money, because a patient spends less time in an intensive-care unit, the hospital stay may be shortened, and the incidence rate for complications that would prolong it is decreased. Unfortunately, such evidence of the cost effectiveness of TDM is buried in the general hospital operating costs and cannot be readily documented.

In these difficult economic times the watchwords are cost containment and DRGs. Thus, departmental administrators within the hospital pharmacy, pathology department, or clinical chemistry laboratory are unwilling to fund the clinical pharmacokinetic service because, even though the expense appears on their operating budget as a debit, the savings to the hospital is not credited to their department. Therefore such a service is not recognized as being cost effective.

Unfortunately, not only the local hospital administrators but also the national health-care economists and politicians who propagate the rules and reimbursement regulations have been unwilling to recognize that the overall decrease in health-care costs that are derived from TDM services are many times greater than the actual costs of providing the service. Thus the role of clinical pharmacokinetics services within our health-care system remains to be resolved.

We, the health-care providers, must develop more-effective strategies for frequency and type of monitoring, to eliminate useless testing. We must communicate with the economists and politicians to ensure cost-effective TDM in every society. I do not have great hope that the administrators and economists will either understand or resolve this issue. In the 1990s, I believe the support of clinical pharmacokinetic services will continue to be minimal.

Quality Control

In the early 1970s, the first external quality-control programs were started within both the United States and Europe, to improve the interlaboratory quantification of antiepileptic drug concentrations. As one looks at the wide variety of commercial controls available in the marketplace today, it is hard to believe that there were then no commercially available controls consisting of drugs in a biological matrix. It was through the pioneering efforts of Utah Laboratories (Canyon County, CA) and Fisher Scientific (Philadelphia, PA) that true biological-matrix controls first became commercially available.

Currently, we run our daily commercial controls and, monthly or quarterly, quality-control materials provided by the various professional organizations (AACC, ASCP, and CAP). We assume that if we achieve the appropriate target range our assays are fine. With few exceptions, there has been no ongoing effort on the part of the external TDM quality-control programs to mimic physiological conditions by adding drug metabolites, other drugs that might be...
administered concomitantly to a patient, or abnormal concentrations of physiological constituents that mimic various disease states and are known to interfere with currently utilized drug assay techniques. The issue is not whether we can hit the target values of a drug-supplemented control sample that has been artificially prepared, but rather whether we can quantify the true drug concentration in our patients' specimens.

Unfortunately, current safety concerns with respect to the presence of HIV, hepatitis virus, etc., in patients' specimens have virtually eliminated the use of pooled patients' specimens as controls by the quality-control programs. Thus we will continue to use commercial controls. We urge the external quality-control programs to expand their efforts to challenge and critique our analytical techniques throughout the next decade. Continuing challenge and education must always be the watchwords of any quality-control program.

**Quality Assurance**

As one reads the new certification requirements of the Joint Committee on Hospital Accreditation and witnesses the changing attitudes, particularly with respect to the issue of quality assurance, it is obvious that clinical chemistry laboratories engaged in TDM must address not only the issues of quality control but also, and perhaps more importantly, those of quality assurance. The new emphasis on quality assurance requires actual clinical follow-up of all inquiries and (or) complaints related to the use of data on drug concentrations in the clinical management of patients. Documentation of laboratory response is essential. The new quality-assurance regulations undoubtedly will improve the TDM services we provide. Perhaps laboratories will now refuse to analyze specimens for digoxin that are inappropriately drawn, i.e., within 8 h of the last digoxin dose. We have high hopes that during the next decade the emphasis on quality assurance will continue to expand and result in better patient care.

**Drug Metabolites**

We say that clinical TDM should constantly be striving to provide more expanded services; we should be assaying new compounds; we should be quantifying drug metabolites; and we should be developing analytical techniques that excel our current ones. This rhetoric all sounds appropriate and achievable when spoken from a podium or written in an editorial. In reality, these goals are difficult—some would say impossible—to achieve.

Drug metabolites represent a classic example of the problem. It is almost impossible for a TDM laboratory to obtain samples of specific drug metabolites; and we should be developing analytical techniques that excel our current ones. This rhetoric all sounds appropriate and achievable when spoken from a podium or written in an editorial. In reality, these goals are difficult—some would say impossible—to achieve.

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Many laboratories tried unsuccessfully for years to obtain samples of cyclosporine metabolites, particularly 17-hydroxy-cyclosporine. The compounds are not commercially available. The drug manufacturer has only limited supplies, which are not available to all who wish to either clinically investigate metabolite profiles or simply establish that they do not interfere with current analytical techniques. It is even harder to obtain the metabolites of drugs for which the patents have expired. During clinical investigations, drug manufacturers usually synthesize only small quantities of metabolites for their own research. When their clinical studies are finished, the supplies are usually exhausted. Currently, pharmaceutical manufacturers do not consider it their responsibility to maintain or distribute drug metabolites to the medical community.

The lack of ready access to drug metabolites precludes practical clinical research, which could be easily performed by liquid- or gas-chromatography. In many extraction techniques both the parent compound and its metabolites are isolated. If the drug metabolites were available as a new drug's use becomes more widespread, it would be possible to ensure that metabolites do not interfere with our analytical techniques. From a clinical perspective, the availability of drug metabolites would allow us to establish metabolite profiles that would accurately phenotype a patient as a fast or slow drug metabolizer and determine his compliance status, and identify which metabolites are altered during drug—drug interactions.

We can rest assured that the pharmaceutical manufacturers are not going to synthesize, stock, and distribute large quantities of drug metabolites for laboratory investigation. From their perspective, the cost of providing such a service is prohibitive. How do we resolve the problem so that we have ready access to drug metabolites? We contact the major organic-synthesis companies (Aldrich, Sigma, Eastman, K & K, etc.) and pay them to synthesize a few grams of metabolite with a clear understanding that they synthesize more than we request, which they can then sell commercially. As an example: I was one of three individuals who contracted with Aldrich Chemical Co. for the original synthesis of p-tolyl phenobarbital as an internal standard for the GLC analysis of phenobarbital. We paid $1000 for the synthesis. Once the original synthesis was worked out, the compound was made commercially available and has been in constant supply for the last 15 years. We would strongly encourage the pharmaceutical manufacturers to provide the "recipes" for synthesizing metabolites to one of the companies specializing in organic synthesis early in a drug's development and perhaps pay for the initial synthesis so that the metabolites can be made commercially available. As an alternative, a group of laboratory investigators could form a cabal and simply pay the synthesis cost every time we need a new metabolite.

This issue must be resolved. Perhaps we should encourage government regulatory agencies to insist that it is the pharmaceutical manufacturer's responsibility to ensure that an appropriate supply of metabolites be made available to investigators, either directly or by providing the procedures for synthesis to the medical community for commercial production. I do not mean to imply that every known metabolite has to be synthesized or that all of a given drug's metabolites need be synthesized. Rather, I would say that the major metabolites should be available to laboratories engaged in TDM, particularly in those situations where metabolite analysis verifies our analytical techniques and (or) leads to a better understanding of the therapeutic applications of the compound.

**Techniques of TDM in the 1990s**

During the past two decades we have witnessed remarkable advances in the technological and analytical aspects of TDM. Few remember that, in 1965, the routine method for determination of phenobarbital and phenylbutazone was a liquid—liquid extraction followed by the Bratton—Morgan coupling reaction. Since that time, we have seen the development of the Syva EMIT system, the Abbott fluorescence polarization TDX assays, the Ames SLIFA and Seralyzer assays and, more recently, the Syntex Medical Diagnostics Acculevel system, which requires no instrumentation in
the usual sense of the word. We are also seeing a swing of routine TDM from the central laboratory to the physician’s office and to the patient’s bedside. I believe that, by the early 1990s, routine TDM as we know it within the central laboratories today will virtually cease to exist. At the present time, prototypes do exist for hand-held TDM instrumentation that accurately monitors drug concentrations. These “TDM ometers” will be as widely used throughout the medical community as hand-held glucometers are today.

This change in analytical techniques will succeed for two reasons: (a) it allows TDM to be performed rapidly, accurately, and efficiently at the patient’s bedside or in the physician’s office, and so the physician can respond to the observed drug concentrations immediately; and (b) it will be more cost-effective than central laboratory monitoring, not necessarily in terms of the actual cost per test but rather in terms of time saved in performing the test, physician–patient contact time, and the adjustment of the patient’s therapeutic regimen to prevent adverse effects or more effectively control the disease process. We tend to say that TDM technology has advanced as far as it can at the present moment. The truth is that the applications of microcomputerization, laser semiconductors, and noninstrumented approaches readily lend themselves to the development of new TDM techniques. By the end of the century, indwelling catheters and (or) sensory monitors will continuously monitor a patient’s drug concentrations.

If TDM as we know it today does go to the patient’s bedside, what happens to the TDM facilities that are now in the laboratory? It is a difficult question. The answer depends on the willingness of the individuals engaged in the discipline of therapeutic drug monitoring today to adapt to change and be innovative. We must aggressively pursue the development of new analytical techniques for those drugs that need to be monitored and for which immunoassays currently are unavailable. There are many frontiers left for TDM to conquer: cancer, mental illness, rheumatoid arthritis, AIDS, etc. In addition, we run the risk that, as TDM goes to the patient’s bedside, our unique analytical techniques and skills will be lost, if we rely on others rather than ourselves to carry out the clinical investigations that are essential for survival. All of these facets are important. However, they will be relegated to a secondary role, because the higher development costs in terms of personal time, with no guarantee of a financial return on the investment, make administrators and department chairmen reluctant to support development projects in the clinical chemistry laboratory.

Robotics represents a viable solution to the economic problems associated with developing and providing new analytical techniques. The pioneering work of Zymark (Hopkinton, MA) has clearly demonstrated the feasibility of robotics in TDM. Their “Zymate II” is a sophisticated yet simple-to-operate robotic system designed specifically for routine analysis of drug concentrations in biological fluids. This system also has the capacity to develop new analytical techniques for specific drugs. It is interesting to note that almost every major pharmaceutical manufacturer utilizes Zymate robotics in the development of assays for the quantification of experimental drugs and their metabolites. Robotics represents a cost-effective approach to the development of new drug assays and provision of routine monitoring services in the hospital TDM laboratory. The unique advantage of this system is that it can operate without supervision on second and third shifts. Robotics can perform the routine mechanical manipulations, thus freeing technologists to engage in activities that require intellectual and cognitive functions.

It is ironic that currently available new TDM techniques have yet to be applied to their full potential. Routine measurement of free drug concentrations is an example. We all recognize that, in general, there is a direct correlation between both total and free drug concentrations and clinical response. Thus, we routinely quantify total drug concentrations. However, there are clinical situations where monitoring free drug concentration clearly is advantageous. This is particularly true in those patients with hypoalbuminemic renal failure or in cases of drug interactions precipitated in patients who are receiving drugs that are displaced from their binding sites by other highly protein-bound drugs, as well as other altered physiological states.

Although the technology for determining free drug concentrations has been available for several years, such determinations are not performed routinely in most hospital laboratories. The laboratories do not measure the free drug, because the physicians do not request them, because they do not know such assays can be easily performed. It is the responsibility of the laboratory to provide special TDM techniques and to educate the physicians in their clinical applications. In the 1980s, the monitoring of free drug concentrations is not going to replace routine monitoring of total drug concentrations. However, information on free drug concentrations is of clinical value in certain situations, and it should be available from every TDM laboratory.

Diagnostic Manufacturers

All of should be very grateful to the manufacturers of TDM diagnostic products. We must always remember that it was they who provided both material and resources to ensure that physicians and other health-care professionals were educated with respect to the value of TDM in providing better patient care. Special thanks go to Syva Company for their efforts from the mid-1970s through the early 1980s and to Abbott Laboratories Diagnostics Division from the early 1980s to the present as the major providers of continuing-education material.

We must continue to have this close and synergistic collaboration between the diagnostics manufacturers and the academic and clinical institutions to ensure that our efforts in continuing education and the development of new analytical techniques move forward. In the 1990s we would hope that the diagnostic manufacturers will be willing to develop assays for new drugs, for which there is clearly a clinical need even though there is not a thoroughly developed market. It is our responsibility to give sound advice and to support the clinical efforts necessary to ensure the success of those tests that we have encouraged the manufacturers to develop.

Medical Technologists in Therapeutic Drug Monitoring

Last spring, I delivered a TDM seminar to about 100 medical technologists at their state convention. As I was lecturing, my curiosity got the better of me. I asked those individuals who knew the half-life of phenytoin to raise their hands. Less than a dozen people raised their hands. I then asked one of them to respond. He said, "24 hours." I asked, "Does it change?" He said, "No." As we discussed
By the conclusion of the lecture, I was both appalled and depressed at the participants' general lack of knowledge with respect to the drugs that they are routinely monitoring every day.

When one talks to medical technologists about analytical techniques, there is no question that they know what they are talking about. They can explain how a TDx operates, they know how to troubleshoot and repair a TDx, but I wonder how many really understand how a fluorescence polarization immunoassay or an EMT assay really works.

A few comments about the future role of medical technologists in therapeutic drug monitoring appear in order. One of the adverse side effects of automation has been an unfortunate change in the perceived image of the medical technologist from a highly skilled professional to simply a button pusher. Medical technologists are the first line of defense against laboratory error, and obviously they should exercise their expertise in ensuring accuracy. Thorough knowledge of the reasons for and interferences with a given assay are essential, not only for accuracy but also for the continued confidence of the medical community in therapeutic drug monitoring.

Automation should be looked upon not as an excuse for rapidly completing the day's workload so the technologist can remain idle but rather as a tool that provides time to pursue other objectives relative to providing better patient care. As clinical chemists and pathologists, we must recognize that the medical technologists who work with us are highly motivated, skilled professionals whose talents and abilities should be used in the development of new analytical techniques and (or) clinical applications. No professional wants to see his or her talents underutilized. To maintain the quality of our medical technologists, we must provide them with the opportunity to participate actively in our efforts to enhance the clinical utility of the services we provide. The professional medical technologist is a key element in these efforts. Technologists' active participation will assure the development of new clinical applications in TDM and applied clinical pharmacology.

Many complain about the changes we have seen in medical technology. The irony is that we do not make the effort to teach the medical technologists what they need to know to be able to take a more active role in therapeutic drug monitoring and participate in the interrelationships between the laboratory and the clinical services, nor do we provide them with the developmental or clinical research information that would encourage them to exercise their own initiative. I believe we must actively discuss unusual cases and results with the medical technologist at the time they are seen. We must encourage them to call such situations to our attention, and, most importantly, we must encourage them to utilize their intellectual expertise in the development of new assays and in the clinical applications of new analytical techniques.

It has been clearly demonstrated that medical technologists with appropriate training do indeed possess the intelligence, skills, and ability to provide interpretive reports of drug concentrations. Children's Memorial Hospital in Columbus, Ohio, has a TDM service in which medical technologists routinely gather information on patients, perform assays, and interpret results to physicians. This program was developed by Ms. Shareen Cox and Dr. Phillip Walson, and it encompasses laboratory medicine, pharmacy, and clinical pharmacology services within the hospital. The program could and should serve as a model for any institution that wishes to utilize medical technologists to the fullest extent of their abilities.

The Future

We all recognize that there are problems within the discipline of TDM that must be resolved, but the potential of TDM to provide better patient care is bright. Throughout the world, there are individuals who recognize the great clinical value of TDM. We must communicate with each other. We must strive to overcome the governmental and political barriers that hinder TDM. We must put aside the petty politics and rivalries that exist within and between various scientific societies. We must encourage young scientists and medical technologists to participate actively in TDM to ensure rational drug therapy. The expertise, the drive, and the will for TDM to succeed is within each of us. We can overcome the current barriers to achieve our ultimate goal—rational TDM that provides the best possible patient care. Let us continue with vigor to ensure the continued success of what we started 20 years ago.