Applied Therapeutic Drug Monitoring

Volume I: Fundamentals

This volume is dedicated to Charles E. Pippenger

Charles E. Pippenger was born on July 12, 1939, in Brook, Indiana. He attended Culver Military Academy and Ball State University, from which he received a B.A. in biology in 1961. One year later he earned an M.A. in biology from Ball State University, with a thesis on "Sex reversal in the domestic fowl." From 1962 to 1965 he was a teaching assistant and research associate with the Departments of Zoology and Neurology at the State University of Iowa, Iowa City, where his research was directed toward the identification of abnormal metabolites and metabolic pathways associated with amyotrophic lateral sclerosis.

In 1965 he was appointed Director of Clinical Chemistry and Biochemical Research Laboratories at New Castle State Hospital, New Castle, Indiana. It was there that he developed an interest in the pharmacological interrelationships between antiepileptic drug therapy and the epilepsies.

He continued his graduate training at Purdue University in 1968 in the Department of Pharmacology and Toxicology, where he studied the relationship between the anticonvulsant effects of hydroxylamine and aminooxyacetic acid on brain γ-aminobutyric acid concentrations in rats and mice. He published his thesis on that subject and received a Ph.D. in pharmacology in 1971 from Purdue University.

From 1971 to 1975, Dr. Pippenger was a research associate in the Department of Neurology at Columbia University, College of Physicians and Surgeons, pursuing research in clinical pharmacology of antiepileptic drugs. He was a pioneer in the adaptation of research techniques to the clinical laboratory and was instrumental in incorporating the homogeneous enzyme immunoassay into routine clinical use for quantitation of antiepileptic drugs. During this period he became aware of the importance and necessity of a high degree of analytical accuracy to apply findings from the field of pharmacology to the clinical setting in clinical therapeutic drug monitoring. He recognized the need for a national program of laboratory quality control, to ensure that all clinical laboratories involved in therapeutic drug monitoring were reporting accurate and reproducible results.

In 1975 Dr. Pippenger was appointed Assistant Professor of Neuropharmacology in Neurology at Columbia University, College of Physicians and Surgeons. That same year, with the support of the Epilepsy Foundation of America, he introduced an international Antiepileptic Drug Level Quality Control Program with 650 enrolled subscribers, the first program of its type in the United States. In addition to assessing the analytical capability of participating laboratories, the program offered educational materials on analysis of antiepileptic drugs and interpretation of antiepileptic drug concentrations.

In 1978 Dr. Pippenger, in association with Raven Press, established *Therapeutic Drug Monitoring*, a peer-reviewed journal dedicated to gathering in one publication current or relevant information from all disciplines to accelerate the exchange of knowledge between clinical and laboratory workers who share a common interest in therapeutic drug monitoring. Coedited with Dr. Alan Richens and published quarterly, the journal contains manuscripts of applied research, clinical applications, reviews, case histories, and methods of interest to the field.

Also in that same year Dr. Pippenger was awarded the Lucy G. Moses prize for outstanding research in clinical neurology by a faculty member at Columbia University.

In 1979 the Antiepileptic Drug Level Quality Control Program became part of a broader program supported by the American Association for Clinical Chemistry: the Therapeutic Drug Monitoring Laboratory Improvement Program. This program, directed at the clinical laboratory to improve the quality of laboratory performance in the field of therapeutic drug monitoring and to educate the laboratory staff, was coordinated by Dr. Pippenger at its inception, and he continues as a resource and guide as the project has expanded to include more than 500 clinical laboratories across the United States.

In 1980, Dr. Pippenger was appointed Associate Professor of Clinical Neuropharmacology in Neurology at Columbia University, College of Physicians and Surgeons. He received the President's Special Award from the American Association for Clinical Chemistry in 1981.

In July 1982, Dr. Pippenger was appointed to the medical staff of the Department of Biochemistry, Division of Laboratory Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, with duties as the clinical pharmacologist responsible for therapeutic drug monitoring.

He currently serves on the Board of Directors of the Epilepsy Foundation of America; the Professional Advisory Board of the New York State Epilepsy Association; the Professional Advisory Board of the New Jersey State Chapter, Epilepsy Foundation of America; the Therapeutic Drug Monitoring Task Force of the American Association for Clinical Chemistry; the Therapeutic Drug Monitoring Research Committee of the College of American Pathologists; and the Committee on Immunoassay Techniques of the National Committee for Clinical Laboratory Standards. He is Editor-in-Chief of *Therapeutic Drug Monitoring* and of the multivolume series, *Handbook of Therapeutic Drug Monitoring*.

Dr. Pippenger makes his home in Cleveland, Ohio, with his wife and two children.

This series is dedicated to him in recognition of his international contributions to the advancement of therapeutic drug monitoring. Dr. Pippenger, the dominant figure in the field of therapeutic drug monitoring, is dedicated to enhancing the laboratory's role through analytical improvement and education of the laboratory staff.

Preface

This volume represents the first in a series of organized presentations of educational material collected by the Therapeutic Drug Monitoring Laboratory Improvement Program sponsored by the American Association for Clinical Chemistry. These chapters have been previously available only to subscribers to the program. The contents of that program were felt to be of sufficient interest to the entire medical community that they are now being made available in book form.

Volume I is a compilation of the manuscripts covering the fundamentals of therapeutic drug monitoring, the basics of pharmacokinetics as it is clinically applied, and a general methods review. Volume II, scheduled for publication in early 1983, will contain detailed reviews and case histories outlining clinical applications of therapeutic drug monitoring data for each of the commonly used antiepileptic, cardioactive, antibiotic, neuroleptic, antineoplastic, and antihypertensive drugs as well as drugs used to treat thyroid disorders and diabetes. Additional volumes of this series will be organized when sufficient materials are collected to present a uniform theme.

As an additional mechanism to reach more laboratories, the Therapeutic Drug Monitoring Task Force proposed this series, a collection of the educational materials presented in a convenient, easy to read format. Because the series is intended to have a self-educating component, a self-assessment questionnaire is included at the end of each volume.

The aspirations of the Therapeutic Drug Monitoring Laboratory Improvement Program remain as delineated by Dr. Pippenger: to provide the clinical laboratory involved in therapeutic drug monitoring a program of laboratory education and improvement. This is done at two levels: (*a*) Samples are submitted monthly for analysis, followed promptly by a histogram report of participants' results; from this the individual laboratories can rapidly assess their accuracy and identify how they perform in comparison with laboratories across the country. (*b*) Monthly mailings of educational materials are directed to laboratory staff, to provide a complete educational program in all aspects of therapeutic drug monitoring. Other programs have quality-assurance functions similar to those of this program: both the Centers for Disease Control and the College of American Pathologists have performed such a function for several years, and the rapid increase in commercial programs offering similar capabilities attests to the popularity and usefulness of this approach. The AACC program is unique, however, in that it combines these attributes with a monthly educational effort intended to improve the participation of the laboratorian.

The Laboratory Improvement Program, conceived by Dr. Pippenger, became a viable program because of the administrative efforts of William Campbell, Ph.D., Executive Director of the AACC, and the willingness of Gordon Newell, General Diagnostics Corporation, to provide the industrial support necessary to produce the quality-control samples that are an integral part of this program. To bring the program to fruition, oversee the administration of the program, and take on the responsibility of procuring the educational material, a Task Force was formed in 1978. Jimmy Standefer, Ph.D., was Chairman, and Drs. Pippenger and Campbell, Jocelyn Hicks, Ph.D., and Henry Nipper, Ph.D., were the original members. In 1979, the Task Force was modified to include Christopher Frings, Ph.D., Thomas Moyer, Ph.D., and Roger Boeckx, Ph.D., to replace Drs. Campbell, Hicks, and Nipper. Paul Orsulak, Ph.D., joined the Task Force in 1980 to provide an expert on the neuroleptic drugs. Danielle Battaglia has served as the Program Director and Diane Breunsbach has been Coordinator since 1979. In 1981, Miss Battaglia became responsible for all AACC educational activities and Miss Breunsbach took over direction of the program. In 1982, Kent Opheim, Ph.D., and Steven Soldin, Ph.D., joined the Task Force to replace Drs. Standefer, Pippenger, and Frings. Each of these individuals has played a significant role in the development and success of the program.

In addition to those mentioned above, we wish to acknowledge the editorial direction of Dr. J. Stanton King, who provided the original manuscript style. Manuscripts have been reviewed for scientific content by laboratorians, researchers, and clinicians too numerous to mention by name. We trust they derive sufficient satisfaction from this educational venture to reward their considerable efforts.

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Related books from the American Association for Clinical Chemistry:

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Effects of Drugs on Clinical Laboratory Tests, Donald Young, L.C. Pestaner, and Val Gibberman, Eds. (Vol. 21, #5)

The Therapeutic Drug Monitoring Program Syllabus
Proceedings from the Four Traveling TDM Programs

The Future of Therapeutic Drug Monitoring, Reprinted from *Clinical Chemistry News*

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I. Fundamentals of Therapeutic Drug Monitoring

1 The Rationale for Therapeutic Drug Monitoring

C. E. Pippenger, Ph.D.

Both physicians and pharmacologists have long been interested in ascertaining why a fixed drug dosage is therapeutically effective in some individuals but not in others. For hundreds of years, appropriate clinical dosage regimens have been established in individual patients by trial and error. Modern technology, however, offers an alternative. Because drug concentrations can be measured in biological matrices, we have now begun to understand the relationship between drug concentration and pharmacologic effect. I believe that history will confirm that one of the greatest advances in pharmacology was the development of analytical techniques for measuring drugs in biological fluids. The ability to correlate concentrations of drugs in plasma, and by inference concentrations in tissues, with the observed clinical effect of a given agent provided new insight into the entire field of therapeutics. Investigators soon established that the desired pharmacologic effect results only if the concentration in plasma exceeds a certain value, and that a certain range of concentrations in plasma is optimum for successful drug therapy. Above this range, undesirable drug side effects can be expected.

The value of therapeutic drug monitoring (TDM) as an adjunct to rational drug therapy in patients with various diseases has been firmly established. Table I lists some drugs that are routinely monitored in many clinical chemistry laboratories to help establish optimal therapeutic regimens for individual patients. For the first time, the physician who monitors a patient's serum drug concentrations is in a position to know why a patient either is not responding satisfactorily to a particular drug dosage or is experiencing side effects to a standard therapeutic dose of a drug. Without question, TDM has significantly improved patient care. For example, more than 80% of all epileptic in-patients presenting different types of seizures can have their disorder controlled with a single drug at appropriate dosages if the concentrations of that drug in plasma are routinely monitored. This contrasts sharply with previous dosage regimens for the epilepsies, which almost invariably involved administration of at least two or three drugs to produce the desired anticonvulsant effect.

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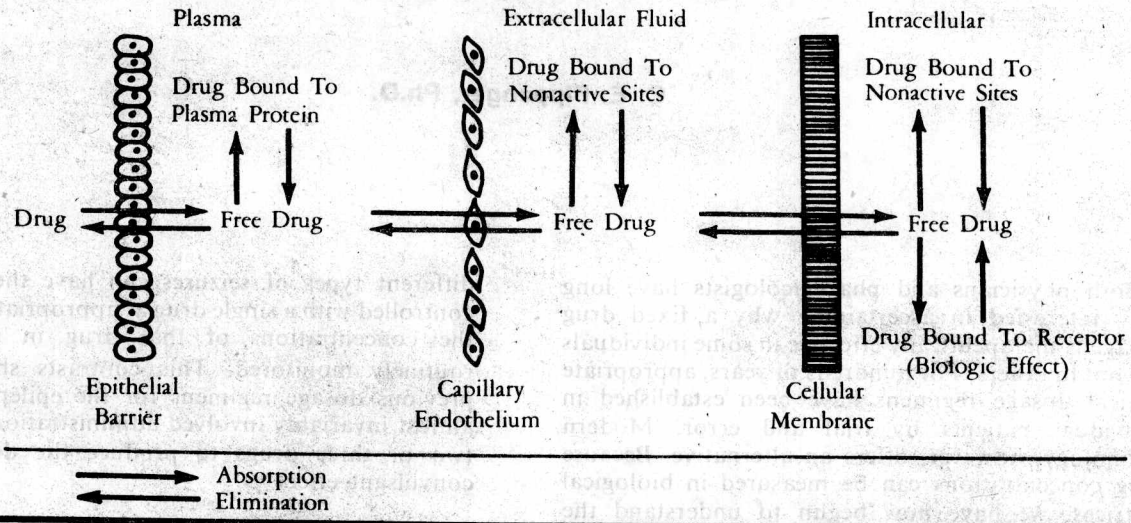
The Rationale for Therapeutic Drug Monitoring

The biological effect of a drug results from the formation of reversible bonds between the drug and tissue receptors that control a particular response. For most drugs, the intensity of a pharmacological effect tends to be proportional to the drug concentration in extracellular fluid. A drug in extracellular fluid can enter tissues and interact with specific receptors to exert biological effects. The exact mechanisms of drug-receptor interactions are not yet clear. For example, antiepileptic drugs are believed to exert anticonvulsant control by binding to nerve membranes or to the receptors associated with nerve transmission to stabilize the neuronal membranes against the excessive electrical activity that generates seizures. The concentration of drug in extracellular water in a given tissue is in equilibrium with the drug concentration in plasma water. Therefore, the concentration of drug in plasma water is an indirect measure of the drug concentration at the site of receptor action. A portion of many drugs is bound to plasma proteins, an equilibrium existing between the part bound to plasma proteins and the part that is free in the plasma water. Only the part that is free can cross the various membranes separating the plasma and extracellular fluid and subsequently concentrate at the tissue-receptor sites (Figure 1). These equilibria of drug concentrations in tissue, extracellular fluid, and plasma water form the basis for monitoring serum drug concentrations in tissues.

It is much simpler to measure total drug concentrations (the sum of free-drug plus bound-drug concentrations) in serum or plasma than to measure free-drug concentrations. Therefore, measurements of

Figure 1. Drug Absorption and Distribution



total drug concentration have traditionally been used to estimate clinical response. It is well recognized that information on the total drug concentration in plasma provides an accurate, although indirect, means of measuring the drug concentration in tissue. Thus, total drug concentration in plasma becomes a measure of potential drug effect. Clinical experiences, as well as a wide variety of clinical pharmacological studies, clearly demonstrate that measurements of drug concentrations in plasma correlate much better with desired clinical effect than does the drug dosage. This is true because such factors as the presence or absence of other disease, differences among patients in their ability to utilize (metabolize) drugs, differences in age and sex, cooperation of patients in taking drugs as prescribed, and potential drug interactions associated with multiple drug therapy, affect the total drug concentrations in the plasma of a patient receiving a therapeutic dosage of a drug.

One of the greatest misconceptions associated with drug therapy is that the dose of a drug administered and its total concentration in plasma are linearly related. That is, that as the total dose of a drug is increased, there will be a concomitant and directly proportional linear increase in the concentration of that drug in the plasma. Thus, if clinical observation indicates that a patient is not showing the desired pharmacological response, it is commonly believed that an increased dose will bring this about. Unfortunately, this is not the case, neither for every patient nor every drug. Measurement of plasma drug concentrations has clearly documented that with certain drugs (such as phenytoin), there is indeed a linear plasma-dose relationship, but only over a given range. When this range is exceeded, a negligible increase in the total daily drug dose will result in a marked increase in its concentration in plasma, an increase completely disproportionate to the administered dose. This phenomenon, known as "saturation kinetics," is a reflection of the limited capacity of some drug-metabolizing enzyme mechanisms. The clinical significance of this phenomenon is that a patient can very rapidly develop toxic effects from a dosage that would not be expected to cause such an effect.

Obviously, trial-and-error treatment regimens do not take into account the wide variability in such things as utilization of drugs, compliance with drug regimen, and disease state. Trial-and-error therapy places both the patient and his physician at the mercy of an unknown factor—the kinetics of the drug in that patient—in the effort to achieve the desired pharmacologic response. Therapeutic drug monitoring can remove the unknown factor by keeping the physician constantly aware of the pharmacologic status of the patient.

Adjustment of a drug regimen to control a clinically evident disease state has a clearcut end point: abolition of the abnormal state. However, drug regimens to control disease states that show only occasional clinical manifestations are much more difficult to evaluate, and in these cases the clinician must largely depend on trial and error to find the appropriate therapeutic concentration of drug; he is never quite sure of success until some time has elapsed without reappearance of clinical symptoms.

A major advantage of therapeutic drug monitoring is that it can predict a therapeutic response by assuring that the concentration of drug is within the optimal therapeutic range, rather than above or

below it. Ultimately the patient benefits, because the probability of an exacerbation of the disease state is decreased when serum drug concentrations are within the optimal range.

Table 1
Optimal Therapeutic Drug Concentrations in Plasma

Drug	Therapeutic Concentration Range*
Carbamazepine	5-12 mg/L
Digitoxin	10-30 μg/L
Digoxin	0.5-2.0 μg/L
Ethosuximide	50-100 mg/L
Lidocaine	1.2-5.0 mg/L
Lithium	0.9-1.4 mEq/L
Nortriptyline	50-140 μg/L
Phenobarbital	10-50 mg/L
Phenytoin	10-20 mg/L
Primidone	6-12 mg/L
Procainamide	4-10 mg/L
Propranolol	40-100 μg/L
Quinidine	2-5 mg/L
Salicylate	200-400 mg/L
Theophylline	10-20 mg/L
Valproate	50-100 mg/L

*These levels represent the optimal range over which the desired therapeutic effect is observed in most patients. It is to be noted that some patients will achieve the desired therapeutic effect at suboptimal plasma concentrations and some will require slightly higher than optimal levels to achieve the desired effect.

But therapeutic drug monitoring is not a panacea. The data must be interpreted in conjunction with the clinical status of the patient. Nevertheless, drug monitoring as a part of routine patient care provides the physician with a valuable adjunctive tool for assessing the pharmacologic status of his patients.

The Clinical Application of Therapeutic Drug Monitoring

There are several advantages to TDM that can be applied to the clinical management of any given patient.

1. *Noncompliance can be identified.* Many patients, particularly those who require long-term drug therapy, tend not to take their medications as prescribed. And patients with a chronic disease that does not necessarily cause pain or other unusual discomfort (for example, the epilepsies or hypertension) may easily neglect to take their medicine. The usual end result of such noncompliance is exacerbation of the existing disorder at some future time.

2. *Individual variations in drug-disposition patterns can be dealt with appropriately.* In any population of individuals, a drug dosage based solely on body weight results in a fixed steady-state concentration in serum that is determined by the various factors regulating the rate of drug disposition in that individual. If the drug concentrations in plasma are measured after a fixed dosage in a large patient population, the distribution of values will be gaussian (a bell-shaped curve). Most patients will show values within the range expected from the total daily drug dosage based on body weight (mg/kg), but those few patients who genetically are either "fast" or "slow" drug metabolizers will have values at extreme ends of the curve. Fast metabolizers therefore require significantly higher maintenance doses to achieve the same concentrations in plasma and consequently the desired therapeutic effect. Conversely, slow metabolizers become drug-intoxicated, and experience side effects from standard therapeutic doses of the drugs; therefore, optimal drug concentrations are maintained in these patients with dosages that are well below those used ordinarily.

Therapeutic drug monitoring allows individuals who are fast or slow metabolizers to be identified, and ensures that their medication regimens can be appropriately adjusted to fit their own metabolic patterns. Without TDM, a prolonged period (sometimes months) of trial-and-error therapy is required to achieve the appropriate dosage regimen, thus unnecessarily subjecting the patient to an interval when the disease process is uncontrolled.

3. *Altered drug utilization as a consequence of disease can be readily identified.* Patients on long-term drug therapy may become acutely ill. Such illnesses may necessitate the administration of additional therapeutic agents. Drug interactions may then cause these patients to respond in an unexpected manner to a fixed dosage of some adjunctive therapy. For example, acute or chronic uremia can dramatically decrease the elimination of a drug that is primarily removed from the body in the urine. In addition, renal failure can alter the protein-binding characteristics of many drugs to plasma albumin. In both situations the ratio of free drug to total drug may increase to the point where free drug concentrations are high enough to produce a clinically evident toxic drug response, although the total drug concentrations are within the optimal therapeutic range for that drug. Hepatic disease can extensively alter a given therapeutic response by impairing a patient's ability to metabolize drugs. Most drug-disposition

processes depend on hepatic "detoxification," to convert the drugs to more water-soluble products that are easily eliminated from the body. Thus, a precipitous rise in concentrations of the parent drug can occur as the unmetabolized drug, which normally would have been eliminated from the system, accumulates during hepatic failure.

In all these cases, and others, therapeutic drug monitoring provides a means of accurately assessing the status of drug disposition at a given time with respect to the ongoing disease process. It is then easy to correct a dosage regimen to coincide with the disease status of the patient. For example, if a patient is in chronic hepatic failure, it may be desirable to administer a drug that ordinarily would be administered daily, such as phenytoin, only once every four or five days, in order to maintain therapeutic concentrations without producing clinical toxicity.

4. *An altered physiological state can be compensated for.* Normal alterations in physiological state also change drug-disposition patterns. Three areas in which TDM is crucial to successful dosage-regimen adjustments should be emphasized.

Recent studies have shown that decreased drug absorption during pregnancy is associated with a dramatic fall in serum phenytoin concentration and exacerbation of seizures in pregnant epileptics. This effect has also been shown for other drugs administered during pregnancy. The use of TDM from the onset of pregnancy, with appropriate dosage regulation to maintain therapeutic drug concentrations, significantly decreases the number of seizures, thus decreasing the prospect of harm to the fetus.

Most importantly, the normal process of maturation involves many physiologic changes that can dramatically alter drug disposition. Children utilize drugs at a faster rate than do adults, and therefore, as a rule of thumb, require almost twice as much drug on a body-weight basis as an adult to achieve the same therapeutic drug concentration. As a child enters puberty, his or her drug disposition patterns rapidly change to those of adulthood. These changes are so rapid that by early pubescence the conversion to adult patterns is essentially complete. Their onset is usually between the ages of 10 and 13, earlier in girls than in boys. It is imperative that TDM be carried out routinely (once every 3-4 months regardless of whether or not the child is seen by a physician) for any drug administered chronically to early pubescent and pubescent children. Failure to adjust the child's therapeutic regimen to compensate for the associated physiologic changes that can alter drug disposition may result in exposure to unnecessary and prolonged drug toxicity, with its attendant sequelae.

Finally, as an individual ages the efficiency of normal physiologic functions again decreases, as does the binding of drugs to plasma protein. Geriatric patients often exhibit diminished rates of drug elimination, thereby requiring lower drug dosages. It is possible for geriatric patients to have total drug concentrations in their plasma that are within the optimal therapeutic range, but their concentration of free drug will be so high as to produce adverse side effects. The clinical signs of drug intoxication in the elderly often present clinically as lethargy and confusion, and TDM provides a means of distinguishing drug-induced confusion from organic deterioration.

The Analytical Aspects of Therapeutic Drug Monitoring

Rapid advances in clinical pharmacology over the past decade are directly attributable to TDM, and the availability of TDM, in turn, is directly related to the rapid advancement in technology associated with the quantitation of drug compounds. When methods of analysis for drugs in plasma became available—colorimetric and ultraviolet spectrophotometric techniques in the late 1950s and early 1960s—the first studies correlating drug concentration with therapeutic effects were done. These procedures required relatively large quantities of serum, extraction techniques that were time-consuming and complex, and the assays were subject to many interferences; therefore drug assays were usually done in research laboratories rather than in routine clinical chemistry laboratories.

Not until the late 1960s did TDM become widespread. Gas-liquid chromatography (GLC) represented a major breakthrough because it provided a method of separating classes of drugs, as well as individual drugs within a class, rapidly and quantitatively at the same time. GLC techniques were further refined and improved so that by the early 1970s GLC measurement of various therapeutically monitored agents was performed routinely in many clinical chemistry laboratories. A major disadvantage of GLC previously had been the complexity of the instrumentation, which necessitated a highly trained and skilled analyst. More recent advances in the development of detectors, particularly the nitrogen-phosphorus detector, have increased the sensitivity of the instruments to such an extent that microsampling by GLC is now possible on a routine basis. Nitrogen detection serves as a successful means of monitoring nanogram quantities of drugs and has been applied to TDM of antiepileptic, antiarrhythmic, and antidepressant drugs.

The development of radioimmunoassay (RIA)

techniques permitted quantitation of drug concentrations in microvolumes of serum. Unfortunately, however, the complexity of the techniques and the necessity of using radioactive materials limited their application to laboratories with special facilities. The lack of RIA assays for a wide variety of drugs has so far prevented widespread application of this technique to routine monitoring.

Making TDM available to all laboratories and physicians required the advent of a simple technology that could be mastered by a technician without special training or instrumentation. This was achieved with the development of homogeneous enzyme immunoassay, which is capable of performing five drug assays on a 50-μL serum specimen. Once the initial daily calibration procedure is complete, each drug assay can be performed in 2 min.

The major advantages of the system are its microcapability and accuracy as well as the rapidity and ease of performance of the assays. The operating principle is based on the ability of the drug-specific antibody to regulate the rate of enzyme activity by formation of a complex with a drug-labeled enzyme. The drug is measured by measuring the rate of enzyme activity.

The disadvantage of the system is that it is limited to those drugs for which antibodies are available. There are many drugs for which antibodies are not available, but which must be therapeutically monitored. The most promising and practical method of monitoring them is by high-pressure liquid chromatography (HPLC). Within the last 5 years this technique has provided laboratories with a system having the same advantages as enzyme immunoassay; it is capable of processing small (100-μL) microsamples, it is rapid and specific, and the instrumentation is relatively simple to operate. In addition, HPLC can be adapted to quantitate a large variety of drugs simultaneously, as well as their active metabolites. HPLC permits simultaneous drug analysis and is a valuable tool for establishing correlations between drug and drug-metabolite concentrations in biological fluids. Obviously, over the next few years HPLC will be even more widely applied in routine TDM.

The Role of the Clinical Chemistry Laboratory in TDM

The expansion of TDM and the increased demand from physicians for such measurements have resulted in a rapid proliferation of these techiques into clinical chemistry laboratories. The major responsibility for routine TDM has shifted from the research laboratory to the clinical laboratory. Its introduction into clinical chemistry laboratories has raised some problems associated with several fundamental aspects of clinical pharmacology, the major one being how much responsibility the analytical laboratory should assume for the actual numbers generated in a TDM situation. Should the laboratory simply report the value that was obtained, or should it provide some assistance to the physician in interpreting it? This is now a highly controversial area. Some laboratories report only the data and leave all matters of interpretation to the physician; others assist the physician in his interpretation by providing supporting data.

I believe strongly that all laboratories engaged in TDM should be in a position to provide supporting information (for example, a review article and/or fundamental data such as dose-response data and biological half-lives) concerning any routinely monitored agent to a physician requesting it. This requires a major effort toward continuing education within the clinical chemistry laboratory with respect to TDM. Basically, any laboratory engaged in TDM should have a working knowledge of clinical pharmacology, particularly with reference to those agents they are monitoring routinely. To this end, I would recommend that the appropriate pharmacology and clinical pharmacology texts (listed in the bibliography) should be available in the laboratory for ready reference. In addition, attempts should be made to provide short courses for both technologists and physicians on the clinical significance of the TDM procedures performed in their laboratories.

Whenever unexpected values are reported from a TDM laboratory, whether excessively high or excessively low, one must attempt to understand the relation between that particular value and the clinical status of the patient. Some factors that can alter serum drug concentrations have already been described. The complexity of drug interactions during concomitant disease, the effect of normal physiologic changes on drug disposition, and individual patient variability in response to a given drug-dosage regimen must all be considered in the physician's interpretation of abnormal concentrations of drugs in the serum being monitored.

One major problem associated with interpreting abnormal values is the laboratory's lack of information about the patient. I strongly recommend the adoption of a universal requisition form for drug-monitoring studies that would contain places for the patient's name, age, weight, sex, a list of *all* drugs the patient is receiving, the total daily dose of each drug, and the time of the last dose. Access to this information, particularly for drugs that are not being analyzed, can save many hours of confusion and painstaking work on the part of the laboratory that is investigating an abnormal drug response. Another aid to the interpretation of abnormal values is the

determination of metabolic profiles, in which the concentrations of both the parent drug and its metabolites are quantitated in either serum or urine.

Conclusion

The role of TDM as an adjunct to the management of patients is firmly established. The number of drugs routinely monitored will continue to grow and the success of this expansion will depend on the continued application and development of both current technologies as well as the development of new ones. Over the next few years, the major technologies for drug monitoring will likely be the homogeneous enzyme immunoassay system and HPLC, because of their reliability and ease of operation. The continuing education of both physicians and laboratory personnel engaged in therapeutic drug monitoring is essential to ensure its expansion and rational application to drug therapy, and its ultimate application to improved patient welfare.

References

Avery, G.S., Drug Treatment—Principles and Practice of Clinical Pharmacology and Therapeutics, Adis Press, Sydney, 1976.

Drayer, D.E. Plasma Assays Help You Manage Drug Therapy, Modern Medicine 45:60-68 (1977)

Fingl, E. Principles of Drug Absorption, Distribution and Metabolism, in Pippenger, C.E., Penry, J.K. and Kutt, H. (eds). Antiepileptic Drugs: Quantitative Analysis and Interpretation, Raven Press, N.Y. 1978, pp. 221-236.

Fingl, E. and Woodbury, D.M. General Principles, in Goodman L. S. and Gilman A (eds) The Pharmacological Basis of Therapeutics Macmillna, 1975, pp. 1-46.

Goodman, L. S. and Gilman, A. G. (eds) The Pharmacological Basis of Therapeutics (fifth edition) Macmillan Publishing Co., Inc. New York, 1975.

Levine, R. R. (ed) Pharmacology: Drug Actions and Reactions (second edition) Little, Borwn and Company, Bostn, 1978.

Melmon, K. L. and Morrelli, H. F. (eds) Clinical Pharmacology—Basic Principles in Therapeutics (second edition) Macmillan Publishing Co., Inc. New York, 1978.

Morselli, P. (ed) Drug Disposition During Development: An Overview, Spectrum Publications, Inc. New York, 1977.

Rowland, M. Drug Administration and Regimens, in Melmon, K. L. and Morrelli, H. P. (eds) Clinical Pharmacology—Basic Principles in Therapeutics, MacMillan, New York 1978, pp. 25-70.

Sheiner, L. W. and Tozer, T. N. Clinical Pharmacokinetics: The Use of Plasma Concentrations of Drugs in Clinical Pharmacology—Basic Principles of Therapeutics (2nd edition), Melmon, K. L. and Morrelli, H. F. (Eds) Macmillan Publishing Col, Inc. New York, 1978.

Sjoqvist, F. Clinical Use of Drug Plasma Levels Determinations, in Azarnoff, D. L. (ed) Yearbook of Drug Therapy—1977, Year Book Medical Publishers, Chicago, 1977.

Sjoqvist, F., Borga, P., and Orne, M. L. W. Fundamentals of Clinical Pharmacology, in Avery, G. S. (Ed) Drug Treatment—Principles and Practice of Clinical Pharmacology and Therapeutics, Adis Press, Sydney 1976, pp. 1-42.

Werner, M., Sutherland, E. W. and Abramson, F. P. Concepts for the Rational Section of Assays to be Used in Monitoring Therapeutic Drugs, Clinical Chemistry, 21:1368-1371 (1975).

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Fundamental Principles of Therapeutic Drug Monitoring

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In my opinion, it is the responsibility of any individual or laboratory engaged in routine therapeutic drug monitoring to have a clear knowledge and understanding of the fundamental principles of clinical pharmacology.

Failure to achieve this understanding results in a laboratory which, though capable of measuring serum drug concentrations, in reality is incapable of providing the necessary supporting information. This information is essential if the requesting physician, and ultimately the patient, is to achieve the maximum benefit from a therapeutic drug monitoring assay.

The biological (pharmacological) effect of a drug dose is due to the formation of reversible bonds between the drug and tissue receptors controlling a particular biochemical response. For most drugs, the intensity and duration of a pharmacological effect is proportional to the drug concentration at the receptor site. The exact mechanisms of drug-receptor interactions remain unclear.

In order for a drug to exert a desired biological effect, it must reach and interact with the receptors regulating that specific response. Figure 1 schematically depicts the factors which can alter the concentration of a drug at its receptor sites.

In addition, other factors—such as age, sex, patient compliance with the prescribed drug regimen, individual differences in drug metabolism and excretion, and drug interactions (particularly during multiple-drug therapy)—contribute to the disposition of a drug within an individual patient, and thus to the observed therapeutic response. Interations between all the potential factors which influence drug therapy account for the broad variation between patients observed in serum concentrations following a single dose of a drug. Individual response to a given drug dose, however, remains constant because the factors which can alter drug utilization within the individual are more or less fixed.

Generally, the probability of achieving a particular blood level from a given drug dose is much less than the probability of obtaining a particular biological effect from a given blood level. This is why administration of fixed doses of a drug to large numbers of patients will produce marked variations in biological response.

With a fixed or standard drug dosage, the desired therapeutic effect will be achieved in some patients. No therapeutic effect will occur in others. And clinical signs of drug intoxication usually associated with drug overdosage will be evident in still others. The titration of drug dosage to obtain a therapeutic plasma concentration can produce the desired biological effect despite the variations between individuals.

Patient Compliance

The most common cause of suboptimal drug levels and consequent failure to achieve the desired therapeutic response is patient non-compliance with the prescribed drug regimen.

It has been suggested that more than 60% of patients do not take their drugs in the manner prescribed by the attending physician. Whenever a patient presents with consistently low serum drug concentrations despite a generally adequate drug dosage, non-compliance should always be considered as the probable cause.

Non-compliance can usually be demonstrated by careful observation of the patient's daily drug intake over a specified interval of time (usually 5 drug half-lives), with frequent monitoring of serum drug concentrations. If the serum concentrations increase over the time interval selected, the patient was non-compliant. If the serum concentrations remain low, other factors such as drug malabsorption or rapid drug metabolism should be suspected.

Drug Absorption

There are three major routes of drug administration: parenteral (intravenous or intramuscular), rectal, and oral.

Parenteral administration is usually encountered only in a hospital or physician's office. The passage of drugs into the general circulation by either the intravenous or the intramuscular route is generally rapid. Parenteral drug administration circumvents the problems associated with oral or rectal administration.

Drug absorption following rectal administration is

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