

Personalized Medicine

Emerging Strategies for Therapeutic Drug Management

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In the conventional approach to pharmacotherapy, physicians prescribe drugs for individual patients but must determine the proper dosage based on the drug's effectiveness in population-based clinical trials. If the drug doesn't produce the desired effect, the dose may be adjusted or a second or possibly even third drug may be prescribed. Optimizing pharmacotherapy may require several months, a process that is very frustrating and expensive to patients and clinicians. For certain therapeutic drugs, particularly those that may contribute to or treat potentially life-threatening conditions, drug and dose selection is guided by monitoring clinical endpoints, or through laboratory monitoring of drug concentrations in blood. For most drugs, however, physicians must rely primarily on clinical expertise and data from population-based studies. If physicians could predict how a patient will respond to a drug and also predict the optimal dosage for individual patients, the process of optimizing pharmacotherapy could be greatly improved and "personalized medicine" could be achieved.

In order for personalized medicine to become a reality, health care professionals will need diagnostic tools that assess the degree of variability in how a patient's body processes a drug—pharmacokinetics—and how a patient's body responds to the drug—pharmacodynamics. Laboratories that provide therapeutic drug monitoring already evaluate pharmacokinetics; however, additional tools would be needed to support personalized medicine, including pre-therapeutic

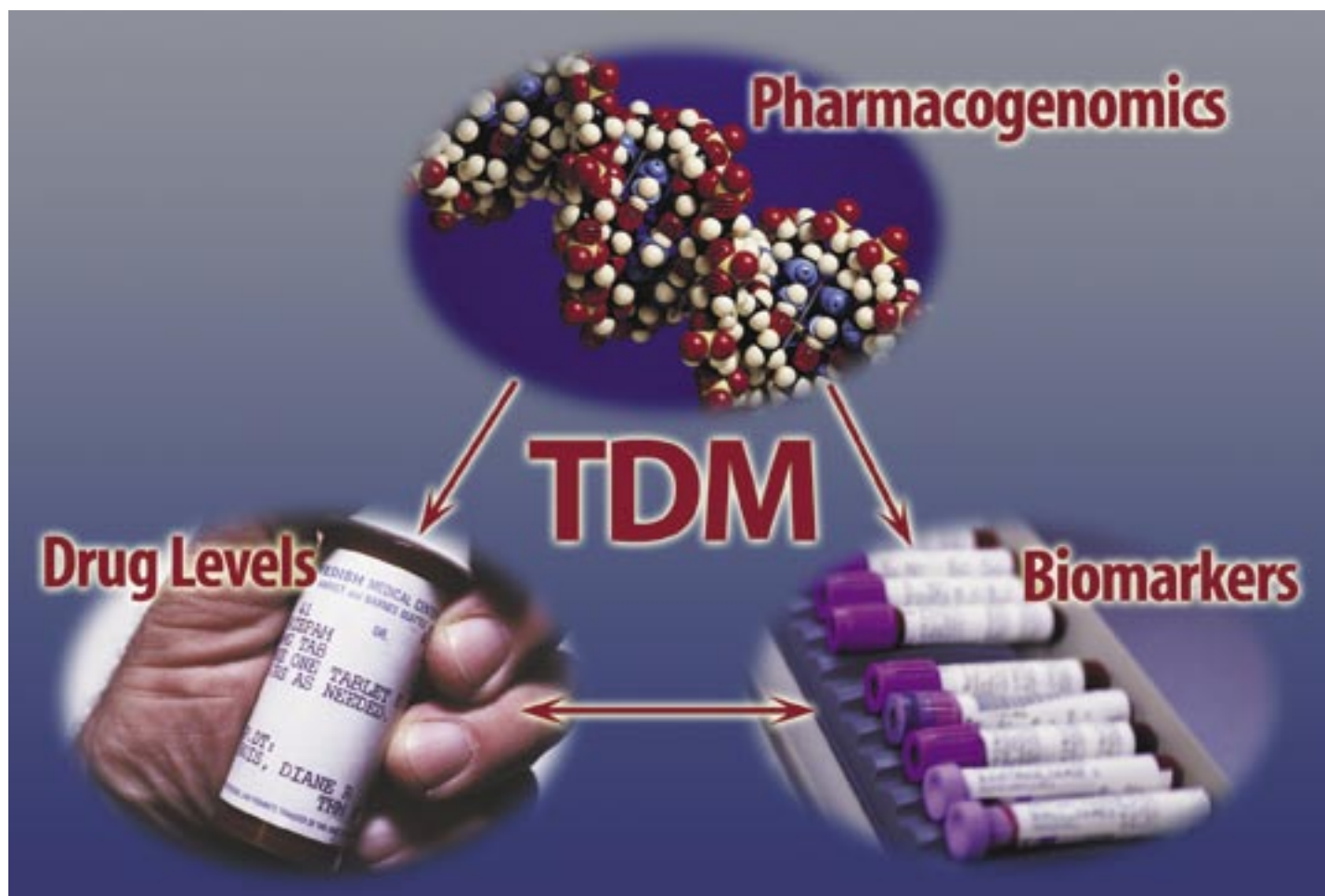
Drug Concentrations in Blood: The Current Approach

Today, therapeutic drug monitoring (TDM) by the laboratory helps ensure that blood concentrations of a drug are within a previously defined optimal therapeutic interval that relates blood concentration within a patient population to the desired clinical effect in that population. Modern TDM began in the early 1970s with gas-liquid chromatographic methods developed by

Although not all drugs are candidates for TDM, many could benefit from TDM if testing was readily available. Good reasons to provide TDM include when a drug has a narrow therapeutic range, when inter-individual differences between circulating concentrations of the drug and the drug dosage are large, when the symptoms of drug toxicity are difficult to discern from the drug indication, when a drug exhibits zero-order kinetics, and when multiple drugs are administered with potential for drug-drug interactions (polypharmacy). TDM can be useful when investigating a lack of drug efficacy in the patient. For example, is the lack of clinical effectiveness due to a pharmacokinetic parameter or to patient non-compliance?

TDM should also be considered when dosing is changed, when new drugs that may interact with existing drugs are introduced, or when patients are not responding appropriately (i.e. toxicity, no or reduced response). Other situations that may impact the pharmacokinetics of a drug, and therefore dictate dosing different from that used for a patient previously, support the need for additional TDM. For example, more frequent monitoring may be needed when patients have a change in their normal physiologic state, for example, during pregnancy or puberty.

Furthermore, recommended dosing guidelines for most drugs are established with adults; however, it is well recognized that drug disposition varies dramatically during life due to changes in body composition, expression of metabolic enzymes, and circulating protein concentrations. In general, neonates clear drugs very slowly, whereas infants and children clear drugs very quickly. During adolescence, metabolic rates may slow abruptly. Children approaching puberty should have potentially toxic drugs monitored frequently until their drug disposition patterns stabilize. Geriatric patients generally require lower doses than adults due to changes such as reduced lean body mass, reduced total body water, increased body fat, reduced drug metabolism, reduced circulating protein concentrations, and reduced renal function.



evaluation of genetic targets associated with pharmacokinetic and pharmacodynamic parameters, more comprehensive post-therapeutic evaluation of circulating drug and/or metabolite concentrations, and measurement of biomarkers that provide objective information regarding drug response. With the availability of these types of diagnostic tools, physicians will be able to minimize the trial and error often associated with pharmacotherapy and employ new strategies that could prevent many adverse drug reactions (ADRs).

Kupferberg (1) and Pippenger (2) to monitor blood concentrations of antiepileptic drugs. Following those initial applications, researchers developed many more methods for TDM based on liquid chromatography and immunoassays. Now, however, the development of new drugs has far outpaced the development of new TDM methods to monitor those drugs. Consequently, a major research focus in the field today is the development of tandem mass spectrometry methods for TDM (3).

TDM is also important for patients that develop pathology. Of particular relevance are conditions that lead to altered renal or hepatic function or protein concentrations. Patients that undergo dialysis or become critically ill may also require more frequent TDM.

The Pharmacodynamic Response: A Shortcoming of TDM

Although the benefits of TDM in pharmacotherapy management are clear, some limitations remain. TDM measures the blood concentration of a drug, which is indicative of an individual's pharmacokinetic variability. Current TDM methods do not account, however, for variability in the pharmacodynamic response, including such factors as individual variations in genes that affect transport of the drug or the targets.

In addition, TDM usually measures only the parent drug. But in many cases metabolites of the drug may be responsible for toxicity or efficacy, making these metabolites a more appropriate analyte to measure. Determining a metabolic ratio using the concentrations of parent drug and a metabolite, or two separate metabolites, could provide an opportunity to evaluate the metabolic capacity of an individual more effectively, but laboratories currently do not perform this type of analysis.

There is also the risk of ADRs in patients whose metabolic response falls outside the norm for a given drug. None of the current TDM tests predicts how a patient will respond to a drug, and therefore they cannot pre-therapeutically avoid an ADR.

The Role of Pharmacogenetics

The goal of pharmacogenetic testing is to predict how an individual will respond to a drug based upon that person's genetic make-up. The target list for potential pharmacogenetic tests includes polymorphic genes that code for any protein that interacts with drugs or drug metabolites. Although most currently employed genes relate to pharmacokinetic processes, some genes also reflect pharmacodynamic parameters, for example VKORC1. Combinations of genes such as CYP2C9 and VKORC1 for warfarin dosing consider aspects of both pharmacokinetics and pharmacodynamics. Such predictive information could then be used by physicians to optimize drug selection and dosage prior to initiating drug treatment. Moreover, specific dosing guidelines based on pharmacogenetic information are already beginning to appear in the peer-reviewed literature and are expected to reduce the number of ADRs (4).

To date, the best studied pharmacogenetic targets are genes that code for drug metabolizing enzymes (DMEs), with the cytochrome P450 isozymes (CYPs) being the most well characterized. Most drugs are metabolized by at least one CYP (see figure). Currently, genetic variants of CYPs can be identified through several commercially-available assays, as well as laboratory-developed assays. However, CYP genotyping methods lack standardization, and unless the entire gene sequence has been determined, detection of all possible variants is unlikely.

Specific genetic variants in CYPs affect the metabolic phenotype through changes in protein expression, structure, function, stability, and/or substrate specificity. Four major phenotypes are described: the extensive or normal metabolizer (EM), poor metabolizer (PM), intermediate metabolizer (IM), and ultrafast or rapid metabolizer (UM). Sequence variants responsible for these phenotypes include single point mutations, insertions and deletions of several nucleotides, and replications and deletions of an entire gene. Researchers have extensively characterized the relationship between the affected protein and the genotype for the CYP variants designated CYP2D6, CYP2C9, and CYP2C19 (5, 6). Clinically significant variants in these genes are common and vary among ethnic groups (see table).

Applying Pharmacogenetic Test Results: The CYPs

Application of pharmacogenetic data depends on the predicted phenotype. Indeed, most drugs are metabolized by multiple CYPs. The simplest clinical application of CYP genotypes to drug selection is for the EM phenotype, since no genotype-based restrictions to drug or dose selection have been established. For the extreme phenotypes—UM and PM—dose reductions, increases, or drug avoidance may be recommended based on whether the CYP activates or inactivates the drug and on the role of alternative metabolic pathways.

Allele Frequencies of Common CYP Variants

Gene	Allele	Predicted Phenotype	Ancestry		
			Caucasians	Asians	African American
CYP2C9	*2	PM	8–14%	<1%	1–4%
	*3	PM	4–16%	2–5%	1–2%
CYP2C19	*2	PM	13–15%	32%	17%
	*3	PM	<1%	5–10%	<1%
CYP2D6	*3	PM	2%	<1%	0–2%
	*4	PM	12–22%	<1%	1–9%
	*5 #	PM	2–7%	5–13%	4–6%
	*6	PM	2%	<1%	<1%
	*10	IM	1–3%	33–51%	6–10%
	*17	IM	<1%	<1%	34%
	x N ^	UM	1–5%	0–2%	0–2%

complete gene deletion

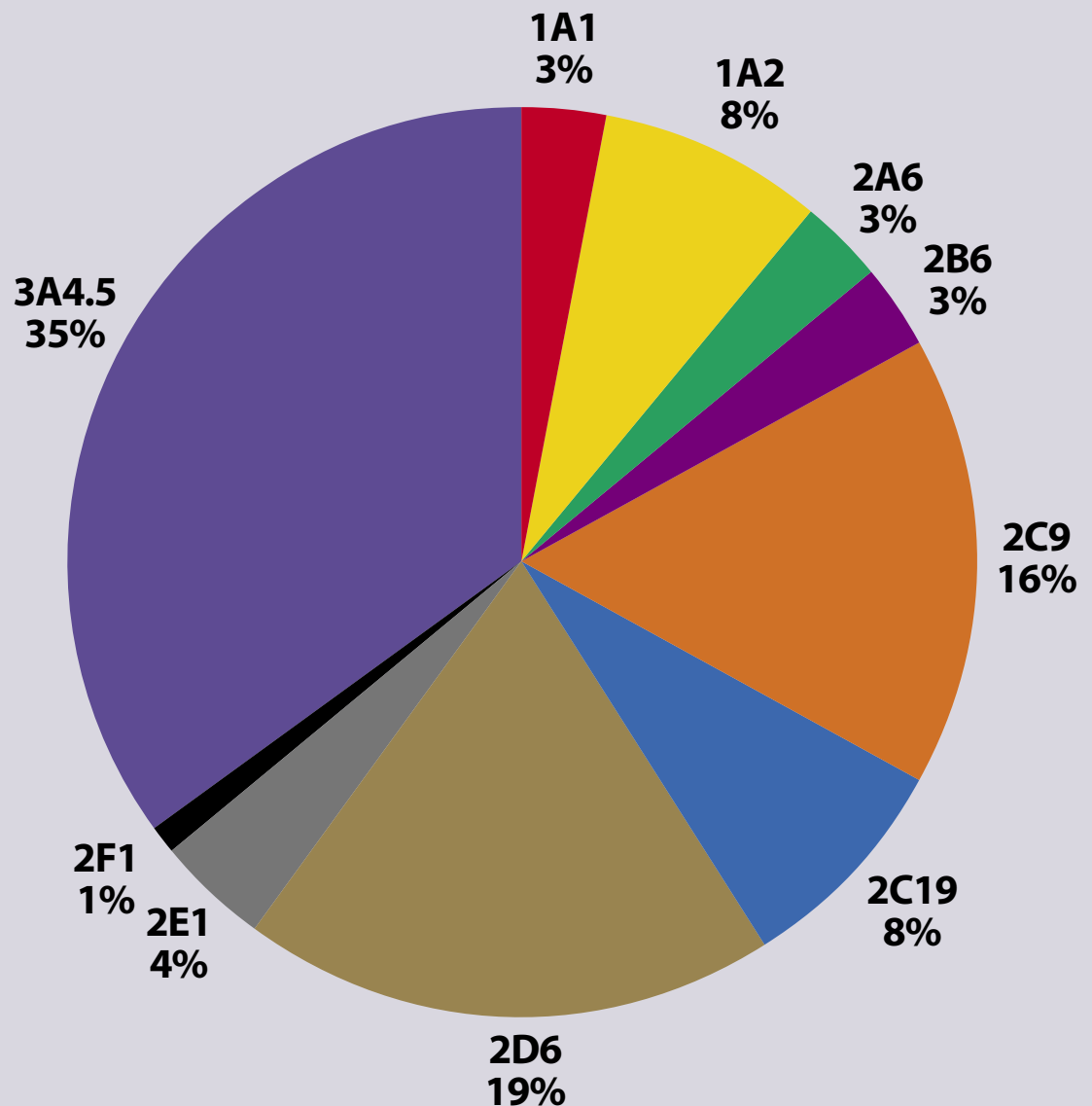
^ more than two copies of EM alleles

Source: Modified from Bradford, L. (2002) *Pharmacogenomics* 3(2):229-243, Mizutani, T. (2003) *Drug Metabolism Reviews* 35(Nos. 2&3):99-106, and Wedlund, P.J. (2000) *Pharmacology* 61:174-183.

Currently, the effect of drug and dose selection on the IM phenotype is unclear due in part to the fact that expression of CYPs is subject to inhibition and induction by a

variety of environmental and physiological factors, and by concomitant medications. An IM may become phenotypically like a PM or an EM based on these variables. In

Proportion of Drugs Metabolized by Common CYPs



This figure illustrates the approximate percentage of drugs metabolized by the members of the cytochrome P450 superfamily. CYP 3A4/52C19, and 2D6 are the predominant enzymes in drug metabolism.

contrast, a PM that does not express any functional enzyme cannot be either induced or inhibited.

Genotype-based dosing guidelines have been published for some medications such as warfarin, antidepressants, antipsychotics, analgesics, and antiepileptic drugs (7–10). Regardless of the CYP genotype, traditional TDM of circulating drug or drug metabolite concentrations will remain important for optimizing drug dosages and assuring compliance with pharmacotherapy.

Other Important Pharmacogenetic Applications

Pharmacogenetic applications involving drug metabolizing enzymes other than the CYPs are also well characterized and clinically important. For example, the risk of toxicity associated with standard doses of 6-mercaptopurine or azathioprine is well correlated with the thiopurine methyl transferase (TPMT) genotype, and genotype-based dosing guidelines have been proposed. Likewise, toxicity associated with standard doses of irinotecan is well correlated with the genotype of a particular uridine diphosphate glucuronosyltransferase (UGT1A1). Recently, the Food and Drug Administration approved re-labeling of irinotecan to suggest dose adjustments when the UGT1A1*28 allele is present, as well as approving a clinical test for detection of that allele. Other UGTs and potentially

other genes may also become important in optimizing dosing of irinotecan (11).

Biomarkers: Indicators of Pharmacodynamics and Toxicodynamics?


Biomarkers for drug management have the potential to provide an objective monitor of an individual's therapeutic response to a drug, a tool that is necessary for true personalized medicine. The definition of a biomarker can be very broad, but in this context we will define it as a biochemical measurement that can be used to determine therapeutic efficacy, extent of toxicity, or individual pharmacodynamics for a therapeutic agent. Some advantages to biological monitoring of therapeutic efficacy include accounting for inter-individual response to therapeutic agents within the target reference range, the ability to account for intra-individual differences in response due to pathophysiologic changes, and the ability to detect sub-clinical responses to therapies when the blood concentration is within the target range. Two examples of biomarkers used to compliment TDM are the use of a cell proliferation assay to monitor efficacy of immunosuppressants in transplant patients (12) and the use of S100A8/A9 to monitor anti-TNF α therapy in patients with rheumatoid arthritis (13).

Biomarkers are also used to indicate toxicity rather than as a measure for therapeutic

efficacy. Common biomarkers predictive of toxicity include β -2-microglobulin for nephrotoxicity and liver enzyme activity for hepatotoxicity. A recent study using biomarkers for management of patients prescribed anti-epileptic drugs (AEDs) examined the correlation of increased urinary N-acetyl-b-D-glucosaminidase (NAG) activity with chronic AED administration (14). Elevated NAG in urine is indicative of tubular injury, and the authors of this study suggest that their results demonstrate that chronic use of AED may alter tubular function even when blood concentrations are within the normal therapeutic interval. Another study (15) examined the role of detoxification enzymatic activity (e.g., erythrocyte glutathione peroxidase, erythrocyte superoxide dismutase) as a biomarker for patients with increased risk of idiosyncratic ADRs with AEDs. Additional work will be required to identify and characterize more biomarkers that predict and support optimization of pharmacodynamics.

A New Strategic Approach to TDM

Truly personalized medicine will require a combination of three considerations—more diverse and readily accessible TDM, pharmacogenetic testing, and biomarker monitoring—to create a whole new approach to effective pharmacotherapeutic management of patients. The emergence of these powerful tools, however, produces almost as many questions as potential applications. How will we design evidence-based studies for validation of these new tools, who will perform the studies, and where will the funding come from? How will this abundance of data be used? How can the laboratory communicate this information effectively to physicians responsible for patient care?

Informatic solutions for data interpretation will need to be developed, and laboratorians will need to put a great deal of thought into the way labs report the data so that clinicians can use it to guide therapy. Many exciting developments appear to be just on the horizon, but considerable work remains to be done before these emerging drug management strategies will be used routinely in a clinical setting. 

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