Fundamentals of Pharmacogenetics in Personalized, Precision Medicine

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KEYWORDS

- Pharmacogenetics • Personalized medicine • Precision medicine
- Pharmacogenomics

KEY POINTS

- Precision medicine is used as it applies to the accuracy of a diagnosis and the precision with which a diagnosis is made.
- Personalized medicine applies to a therapeutic approach tailored to optimize a therapy specific to an individual as contrasted to a group of individuals.
- Pharmacogenetics (PGx) is used to denote clinical testing of genetic variation to assess response to drugs. PGx is an integral component to both precision medicine and personalized medicine.

PERSONALIZED AND PRECISION MEDICINE

What is "precision" medicine and does it differ from "personalized" medicine? Although these 2 concepts have operationally different definitions, they complement each other in application. "Precision" medicine is used as it applies to the accuracy of a diagnosis and the precision with which a diagnosis is made. In essence, precision medicine is linked to the definition of a true disease state and to understanding pathologic mechanisms.[1] With regard to a laboratory test, the concept of "clinical validity" as defined by agencies and professional organizations is a good analogy as to how well does the test result define a condition of interest.[2]

Personalized medicine applies to a therapeutic approach tailored to optimize a therapy specific to an individual as contrasted to a group of individuals.[1] The concept

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of a personalized approach to therapy has been used since the inception of modern medical practice. Examples are in the selection of blood products for transfusions and of matched tissues for transplantation, both based on biochemical information specific to the donor and recipient. Advances in technologies have increased the precision with which we can tailor a specific therapy to a particular individual. These advances have created emphasis on the concepts of personalized and precision medicine and, although they have different definitions, they enable each other in practice. One application that has greatly improved the personalization of therapeutics is the introduction of pharmacogenetics (PGx) as a subdiscipline in laboratory medicine. To appreciate this laboratory discipline it is important to understand basic elements of pharmacology applied to clinical practice.

OVERVIEW OF THERAPEUTIC DRUG MONITORING, PHARMACOLOGY, AND PHARMACOGENETICS

Therapeutic drug monitoring (TDM), or more recently referred to as therapeutic drug management, involves using measured serum drug concentrations along with pharmacokinetic (PK) and pharmacodynamic (PD) principles to optimize a patient's response to drug therapy. The response to drug concentrations may be therapeutic, subtherapeutic, or toxic, and these depend on considerations involving both PK and PD. The aim is to optimize therapeutic response by maintaining serum drug concentrations within a therapeutic range (the concentration at which the drug maximizes effectiveness and minimizes toxicity). TDM is applied most effectively to a small number of drugs with a narrow range of safe and effective serum drug concentrations. **Fig. 1** shows the conceptual relationship among dose rate, PK, serum drug concentration, and pharmacologic response.[3] The health care provider will determine the dose and frequency of drug administration, typically based on the drug's known bioavailability and clearance rate, which will result in steady-state serum concentrations that provide the expected therapeutic response. Examples of drugs that typically are monitored using TDM principles are amikacin, amitriptyline, carbamazepine, cyclosporine, digoxin, gentamicin, imipramine, lidocaine, lithium, methotrexate, nortriptyline, phenytoin, theophylline, tobramycin, valproic acid, and vancomycin, among others.

Pharmacology is the study of drugs and how the function of living tissues and organisms is modified by the effect of drugs and other chemical substances. Historically, knowledge of pharmacologic responses to drugs has been based on average population responses. Gene-based technologies provide information specific to an individual's drug

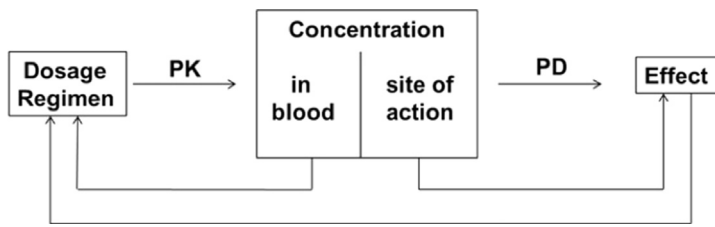

Fig. 1. Conceptual relationship between PK and PD. PK relates to the effect of the body on the drug and principally includes bioavailability, distribution, and clearance. PD relates to drug concentration and receptor availability. The net effect is dependent on both PK and PD. (*Adapted from* Linder MW, Valdes R Jr. Pharmacogenetics: fundamentals and applications. Therapeutic drug monitoring and toxicology. vol. 20(1). Washington, DC: AACC; 1999. p. 9–17; and Burtis, et al. Tietz textbook of clinical chemistry. Philadelphia: W.B. Saunders; 1999.)