REVIEWS

Moving from Basic Toward Systems Pharmacodynamic Models

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ABSTRACT: Building upon many classical foundations of pharmacology, a diverse array of mechanistic pharmacokinetic–pharmacodynamic (PK/PD) models have emerged based on mechanisms of drug action and primary rate-limiting or turnover processes in physiology. An array of basic models can be extended to handle various complexities including tolerance and can readily be employed as building blocks in assembling enhanced PK/PD or small systems models. Our corticosteroid models demonstrate these concepts as well as elements of horizontal and vertical integration of molecular to whole-body processes. The potential advantages and challenges in moving PK/PD toward systems models are described. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2930–2940, 2013

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INTRODUCTION

The areas of pharmacokinetics and pharmacodynamics (PK/PD) have evolved from a long history of appreciation of basic pharmacological principles mostly applied to static or *in vitro* systems. An array of simple PK/PD models for the time course of *in vivo* drug effects have evolved to the present era of use of extended or enhanced PK/PD models and small-to-large systems models to capture drug actions at various levels of biological organization. This overview will describe the various arenas that have embraced PK/PD and pharmacometrics, highlight major concepts and features of commonly used PK/PD models, demonstrate model-building approaches leading to enhanced PK/PD and small systems models, and indicate the complications faced in evolving better quantitative methods for larger systems models.

Evolution of PK/PD and Pharmacometrics

The recognition that new mathematical relationships were needed to extend basic pharmacologic equations from static systems to *in vivo* time courses of drug effects began in 1965 [1] with the Levy "$k{\cdot}m$" equation that provided the connection between PK (the k reflecting the monoexponential elimination rate constant) and pharmacology (the m being the mid-range slope of the Effect versus log drug concentration function). Gerhard Levy has been viewed as the "Father of Pharmacodynamics" for this and his many later contributions to PK/PD. Subsequently, with simulation studies, Wagner[2] popularized the use of the Hill Function and demonstrated the value of "signature profiles" (my term) to portray basic expectations of simple PK/PD functions.

These early contributions have blossomed into wide acceptance with many advancements in theory, and numerous applications of PK/PD and pharmacometrics in the pharmaceutical industry, government regulation, research institutes, and academia. The recent review by Lalonde et al.[3] describes the utilization of modeling and simulation in the pharmaceutical industry pointing out how quantitative pharmacology can be implemented in each phase of drug development. The US Food and Drug Administration embraced PK/PD in the early 1990s and both early and recent reviews by the leadership of Peck, Lesko, and Gobburu[4–7] provide perspectives on how pharmacometrics has impacted the search for safer and more efficacious drugs in more efficient and timely fashion. The National Institutes of Health (NIH) held a meeting in 2002 to assess training needs in the

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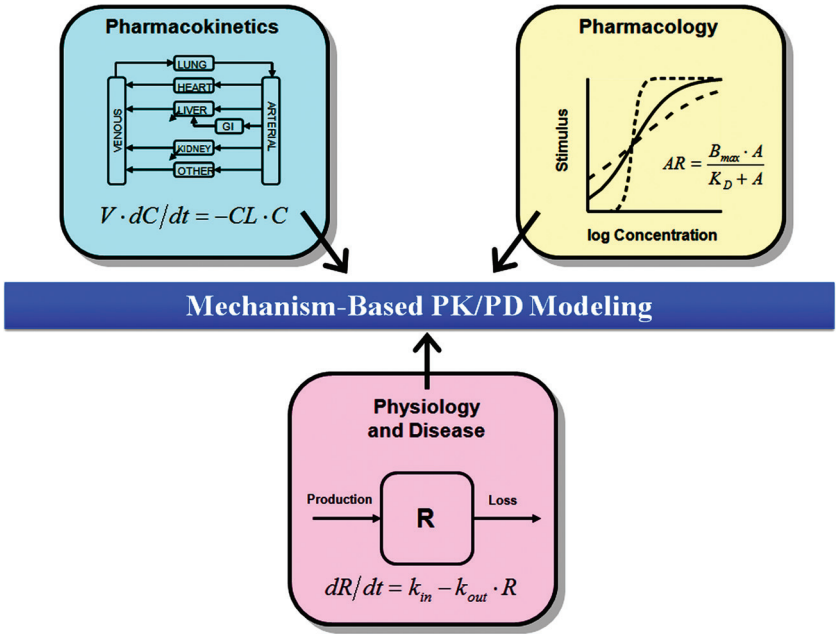

Figure 1. Mechanism-based pharmacokinetic–pharmacodynamic (PK/PD) models typically integrate the time course of drug concentrations (PK) including biophase distribution, the nature of drug–target interaction (Pharmacology), and turnover processes reflecting the relevant physiology and disease.[12]

pharmacologic sciences. They concluded, "There was a remarkable consensus that the core subject matter of pharmacology remains the principles of pharmacokinetics and pharmacodynamics."[8] This area is now widely taught, especially in Schools of Pharmacy. The NIH sponsored two recent symposia bringing together PK/PD modelers and system biologists and pharmacologists to consider the state-of-the-art and future of quantitative and systems pharmacology (QSP). This resulted in an extensive "white paper"[9] that will hopefully lead to improved funding and new research.[10] Accompanying these avenues of advancement of PK/PD has been the evolution of computational power and software programs such as WinNonlin, NonMem, Adapt, and many others. Numerous small companies provide consultation, data analysis, simulations, and pharmacometric reports for both the Pharma and generic companies. Led by the 1973 appearance of the *Journal of Pharmacokinetics and Biopharmaceutics* (now *Pharmacodynamics*) edited by Sidney Riegelman, Leslie Benet, and Malcom Rowland (I am currently Editor-in-Chief), the number of journals and published articles in quantitative pharmacology has exploded over the past 50 years. Journal articles that include "Pharmacodynamics" in the title in recent decades number in MEDLINE[11] as follows: (1963–1972) 153, (1973–1982) 255, (1983–1992) 970, (1993–2012) 1564, and (2003–2012) 1772. Numerous scientific meetings include PK/PD and QSP topics and symposia. Several series of PK/PD specialty meetings have promoted the field including those hosted by David D'Argenio (Biomedical Simulation Resourse) in Los Angeles, Meindert Danhof in the Netherlands, the American Conference on Pharmacometrics, and the Population Approach Group Europe (PAGE) meetings. Recently established was the International Society of Pharmacometrics (www.go-isop.org).

Basic Mechanism-Based PK/PD Models

Most "mechanism-based" PK/PD models include some recognition that one or more critical steps in drug action are controlled by the PK, receptor or target binding mechanism, and/or physiology including homeostatic and disease mechanisms yielding resolvable parameters for the major rate-limiting process(es). These three main components are depicted in Figure 1.[12] The applications of such models can be described as a "top-down" approach where the modeler should gain appreciation of the underlying PK, pharmacology, and physiology in ascribing a general model and designing studies and analysis of experimental data. The models typically seek parsimony. Model parameters are expected to have strong statistical reliability and relate to underlying processes (e.g., production or clearance of endogenous substances). Systems models, on the other hand, are "bottom up" in configuration with a wealth of equations and assumed parameters and are used for simulation purposes seeking to match expectations with profiles of experimental data and for exploratory purposes.