Chapter 8
Foundations of Pharmacodynamic Systems Analysis

William J. Jusko

Abstract The pillars of pharmacodynamic modeling are the pharmacokinetics of the drug, the nature of the pharmacology that underlies drug interactions with their targets, and the physiology of the system considering molecular to whole body levels of organization and functioning. This chapter provides a general assessment of the fundamental components and some interactions of each of these pillars indicating how they serve as building blocks for systems models. Key elements of pharmacokinetics include the operation of Fick's Laws for diffusion and perfusion along with the often nonlinear mechanisms of drug distribution and elimination. Target-binding relationships in pharmacology evolve from the law of mass action producing capacity-limitation in most operative control functions. Mammalian physiology and pathophysiology feature a wide breadth of turnover rates for biological compounds, structures, and functions ranging from rapid electrical signals to lengthy human lifespans, which often determine the rate-limiting process and basic type of model to be applied. Appreciation of the diverse array, mechanisms, and interactions of individual components that comprise the pillars of pharmacodynamics can serve as the foundation for building more complex systems models.

Keywords Fick's laws · Target-binding · Drug-biological interface · Affinity · Capacity · Substrate control · Operational efficacy · Turnover · Homeostasis · Gaddum equation

8.1 Introduction

The three pillars of pharmacodynamics (PD), as depicted in Fig. 8.1, are the pharmacokinetics (PK) of the drug, the pharmacology and mechanism of the drug-biological interface, and the physiology or pathophysiology of the system

W.J. Jusko (✉)
Department of Pharmaceutical Sciences, University at Buffalo,
404 Kapoor Hall, Buffalo, NY, USA
e-mail: wjjusko@buffalo.edu

D.E. Mager and H.H.C. Kimko (eds.), *Systems Pharmacology and Pharmacodynamics*,
AAPS Advances in the Pharmaceutical Sciences Series 23,
DOI 10.1007/978-3-319-44534-2_8

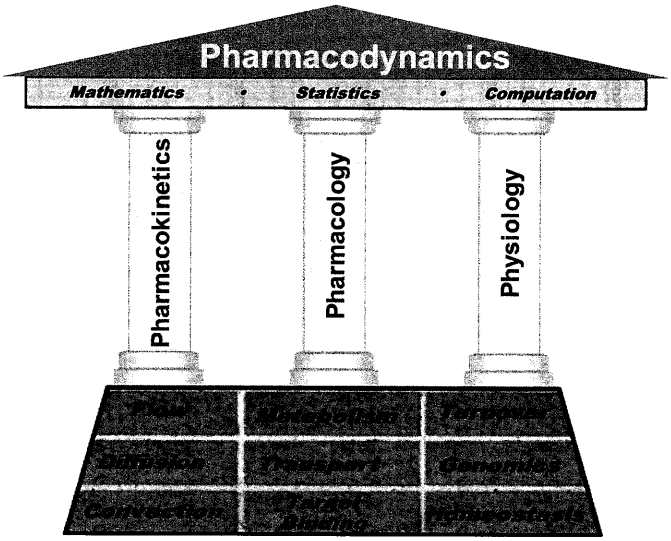

Fig. 8.1 The palace of pharmacodynamics with its foundation, structural components, and three pillars

being altered by the drug (Mager et al. 2003; Jusko 2013). Each can contribute to the extent and time-course of observed pharmacodynamic responses depending on their intrinsic properties and rate-limiting step(s). The foundations of systems analysis will be explored by delineating the basic "rules of biology" for the major components that govern each of the pillars of pharmacodynamics. Along with the determinants of PK, two general principles, namely capacity-limitation and turnover, form the basis for a variety of commonly used PK/PD and systems models. Genomics is included in Fig. 8.1 as the presence, location, and functioning of determinants of PK/PD are governed by genomics and genetics. The quantitative skills of mathematics, statistics, and computation are needed to identify relationships, integrate them into models, analyze experimental data, and perform simulations.

8.2 Pharmacokinetics

Common approaches for analyzing pharmacokinetic data utilize noncompartmental, compartmental (mammalian), and physiological concepts and methods, with ascending degrees of complexity. Physiologically-based PK (PBPK) models provide mechanistic and insightful separation of drug and systems properties as well as their interfaces and interactions. Three key relationships that underpin drug distributional processes in PBPK models are:

$$\text{Fick's Law of Diffusion:} \quad \frac{dA}{dt} = PS(C_h - C_l)$$

where the rate of drug movement (Amount/time, *dA/dt*) from higher (C_h) to lower (C_l) concentrations is governed by the permeability-surface area (*PS*) coefficient (Fick 1855). Permeability (*P*) is governed by molecular size and lipid solubility of the compound along with the nature of the biological membrane and its surface area (*S*). This equation is often invoked to describe small molecule (drug) absorption rates, movement between interstitial fluids (ISF) and cell water spaces, and has been adapted to account for biophase distribution of drugs.

$$\text{Fick's Law of Perfusion:} \quad \frac{dA}{dt} = Q(C_a - C_v)$$

where the rate of organ uptake (*dA/dt*) is governed by arterial (C_a) and venous (C_v) drug concentrations and organ blood flow (*Q*) (Teorell 1937). The ratio of $(C_a - C_v)/C_a$ is also termed the Extraction Ratio (*ER*). This equation is commonly used in PBPK models to describe drug distribution to various organs and tissues via blood flow.

$$\text{Convection:} \quad \frac{dA}{dt} = L(1-\sigma)\cdot C = f_L \cdot Q(1-\sigma)\cdot C$$

where organ uptake of molecules is determined by water movement equaling lymph flow (*L*) and the vascular reflection coefficient (σ) associated with water flux across capillary membranes into ISF (Renkin 1979). Lymph flow is usually assumed as a small fraction (f_L = 0.02–4 %) of blood flow to each organ or tissue as determined by the Starling (1896) approximation, while the reflection coefficient varies with type of organ capillaries (some 'leaky' such as liver, some 'tight' such as muscle). This equation is used in PBPK models of monoclonal antibodies (mAbs) and other large molecules to describe their limited and slow movement from plasma to ISF (Cao et al. 2013). Glomerular filtration rate is primarily a convection process as well.

The joint roles of blood flow and permeability for control of the distribution of molecules from blood to tissues is termed Distribution Clearance (CL_d) in PK and quantified as:

$$CL_d = f_d \cdot Q = Q\left(1 - e^{-PS/Q}\right)$$

where f_d is the fraction of *Q* accounting for organ uptake of drug, *PS* is the rate-limiting factor when *Q* is small, and *Q* is the rate-limiting factor when *PS* is large (Stec and Atkinson 1981).

The array of nonlinear protein binding, metabolism, transport, and clearance relationships commonly encountered in PK are listed in Table 8.1 (Jusko 1989).

Table 8.1 Common capacity-limited functions in pharmacokinetics

Process	Function	Equation	Capacity	Affinity	Substrate	References
Metabolism	Metabolite (M) formation rate	$\frac{dM}{dt} = \frac{V_{max} \cdot C}{K_m + C}$	V_{max}	K_m	Concentration	Michaelis and Menten (1913)
Transport	Flux	$\frac{dA_T}{dt} = \frac{V_{max} \cdot C}{K_m + C}$	V_{max}	K_m	Concentration	Shannon (1939)
Protein binding	Bound drug	$D_b = \frac{n \cdot P_t \cdot D_f}{1/K_A + D_f}$	n: No. Binding Sites P_t: Protein Conc.	K_A: Equilibrium Association constant	D_f: free drug	Goldstein, (1949)
Organ clearance	Clearance	$CL = \frac{Q \cdot CL_{int}}{Q + CL_{int}}$	Q: Blood Flow	CL_{int}: Intrinsic clearance	Concentration	Rowland et al. (1973) and Wilkinson and Shand (1975)

They all evolve from the law of mass action where the limited quantity of binding substances, metabolic enzymes, or transporters results in capacity-limited processing of drugs and other substrates. At low drug concentrations, the functions operate linearly, such as with the common relationship for intrinsic clearance, $CL_{int} = V_{max}/K_m$, pertaining to drug metabolism. Often the preferred or operative drug concentration is the free or unbound drug in either plasma or in tissues. These distributional and elimination relationships are components of full PBPK models and are presented here partly owing to their fundamental value in PK, but also because they are helpful in describing the kinetics of physiological substances or biomarkers when analyzed in PK/PD and systems models. For example, the PK/PD modeling of cortisol as an indicator of adrenal suppression and of nitrate as a biomarker of inflammation is best handled by considering their intrinsic kinetics (Krzyzanski and Jusko 2001; Sukumaran et al. 2012).

8.3 Pharmacology

The interaction of drugs (D) with their biophase targets (R) is the interface that controls the array of subsequent genomic, proteomic, biochemical, and physiological changes. These targets may be receptors, enzymes, transporters, ion channels, and/or DNA. A common feature is that the concentration or quantity of such targets is limited and can be described with the law of mass action:

$$D + R \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} DR$$

as described by:

$$\frac{dR}{dt} = k_{on} \cdot D \cdot R - k_{off} \cdot DR$$

where k_{on} is the association rate constant, k_{off} is the dissociation rate constant and, at equilibrium, the equilibrium dissociation constant is $K_D = k_{off}/k_{on}$. This type of interaction leads to a nonlinear relationship that the author calls "The Equation of Life":

$$Function = \frac{Capacity \cdot Substrate}{Affinity + Substrate}$$

In this fashion, *Capacity*, *Affinity*, and *Substrate* control numerous biological processes: those involved in PK as listed in Table 8.1 and those describing many pharmacological actions as listed in Table 8.2. These pharmacologic processes or

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.