“Quantitative Pharmacology: An introduction to integrative pharmacokinetic-pharmacodynamic analysis”

Reviewed by PJ Lowe

What is “Quantitative Pharmacology”? Surely, pharmacologists have long quantitated responses through parameters such as ED$_{50}$ or EC$_{50}$, the dose or concentration for half-maximum effect, seeking to understand the influence of many factors, whether they be drug structure or patient-disease related. In “Quantitative Pharmacology,” Gabrielsson and Hjorth explain that it is the integration of key time-dependent processes in vivo: pharmacokinetics (PK; absorption; distribution to target and other sites; binding to target and nonspecific entities; elimination) and pharmacodynamics (PD; target binding driving system–related responses, whether in parallel or a causal series). These fit together in the context of how, after a lead candidate is discovered, a drug should be optimized by taking account of all aspects to be successfully developed as a marketable product.

Beyond the introduction, there are six further chapters. In “Kinetics from a PD point of view,” the essentials of clearance (CL) and multicomartmental behaviors are covered, including a diagram well illustrating the filling and emptying of compartments in the initial and terminal phases of plasma drug concentration–time profiles. From a PD point of view, the concept of the “effective half-life” of a compound is important, i.e., that which covers the majority of the exposure (aka area under the curve). Perhaps, there should be a renaissance of the mean residence time, the effective half-life being this multiplied by log$_2$(2).

In “Plasma protein binding,” the hypothesis for the unbound drug being the driver of PD responses is presented. From a discovery point of view, compounds should not only be optimized for target binding potency but also for low unbound CL to maximize tissue equilibrating unbound drug concentrations. In the end, it is the trade off between potency (e.g., $K_i$), the fraction unbound ($f_u$), and CL which must be optimized.

In “Dose, time and flow dependencys,” potential nonlinear and non-time constant properties are explored. This includes forms of target-mediated drug disposition (including Michaelis–Menten saturable elimination), saturable transfer processes (e.g., absorption), and time-dependent changes such as induction of metabolism. Not forgetting, of course, that plasma protein binding can also be nonlinear and non-time constant.

In “Rapid concentration–response equilibria,” pharmacological concentration–effect relationships are introduced, including linear, logarithmic, exponential, and sigmoid $E_{max}$. Also explained are experiments to generate appropriate data and how to decide between candidate models. Examples are given of how species differing concentration–response can become similar once unbound drug concentrations are used. Slightly perplexing is the example with brain receptor binding, with the unexplained appearance of a $K_{on}$ parameter to enable the estimation of the half-life of receptor dissociation from $K_{off}$. All previous presentations used an equilibrium $K_i$. Perhaps, this is from the next chapter.

In “Time delays between plasma concentration and response,” three classes of PD model are described: distributional delay, turnover delay (aka indirect response), and receptor on/off. These are well illustrated with clear graphics. The example in which PKPD modeling was used rather than direct summarization of washout data was interesting as it changed conclusions regarding safety margins. Of note was the example in which a “hit-and-run” single time point dose–response study design caused a 100% bias in the potency estimate of a candidate. Clearly, the authors advocate complete, integrative, time series PKPD analyses, i.e., “Quantitative Pharmacology” approaches.

Finally, in “Inter-species scaling,” information is integrated to scale preclinical PKPD models to man. The core steps are (i) scale PK (only CL if steady-state concentrations required), (ii) translate
pharmacology between species through unbound concentrations; if PD turnover required, scale by bodyweight to \( \frac{3}{4} \) power; (iii) combine scaled PK and PD to produce a human dose prediction. However, importantly for human safety, there is step (iv) which allows for uncertainty, the potential to be wrong, by giving ranges (e.g., half and double) of possible predicted CLs and effective unbound plasma concentrations.

Overall, this book is an easy introduction to “Quantitative Pharmacology.” I read cover to cover in two sessions plus a day’s travelling, without my eyes drooping. If you are a nonkinetically minded research pharmacologist, medicinal chemist, physician, veterinarian, or statistician, and are curious about what PKPD experts and modelers are up to and what they can deliver, it is well worth reading.

Conflict of interest: The author declared no conflict of interest.