Commentary

Theme: Landmark Publications in the Pharmaceutical Sciences: The Backstory
Editor: Ho-Leung Fung

Holford NHG and Sheiner LB “Understanding the Dose-Effect Relationship-Clinical Application of Pharmacokinetic-Pharmacodynamic Models”, *Clin Pharmacokin* 6:429–453 (1981)—The Backstory

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My personal interest in understanding the dose–concentration–effect relationship started during my medical student training at the University of Manchester in England. In 1967, the Department of Pharmacology introduced a 1-year Bachelor of Science degree which medical students could take between their second and third years of the medical course. Only two students applied and that is how I was accepted for an intensive, practical course in pharmacology. One of the first laboratory sessions was to study the contractions of a segment of guinea pig ileum in response to acetyl choline (Fig. 1). This taught me the difference between dose and concentration, the asymptotic nature of the concentration–effect relationship, and the often inexplicable variability of biological systems (What happened to the response at 16 ng/mL?).

But there was more than many hours in the pharmacology laboratory. My mentor, Bob Foster, insisted that we read the literature and one paper that stood out was by Arunlakshana and Schild (1). This paper described the quantitative basis for describing concentration–effect relationships including the action of competitive and non-competitive antagonists. I still recall my struggles to understand the mathematics. Mathematics has always been a weakness for me. I did so badly at mathematics at school that I could not go to university to do physics as I wished but had to learn some biology so I could get into medical school.

Now fast forward to 1975, I arrived in California with 3-years training in internal medicine and the offer of a fellowship in clinical pharmacology at the University of California at San Francisco. Within weeks of my arrival, I had been taught by Malcolm Rowland, Les Benet, Sid Riegelman, Tom Tozer,

Wolfgang Sadée, and Lewis Sheiner. I did not realize until many years later that I was at the epicenter of an explosion of pharmacokinetic and pharmacodynamic thinking.

Sid Riegelman had a grant from the FDA to study the bioavailability and bioequivalence of quinidine formulations. He asked me to be the medically qualified person to take responsibility for the clinical aspects of the study. Quinidine concentrations were the responsibility of Peter Coates and Theo Guentert, who later became key leaders of clinical pharmacology in the European pharmaceutical industry. I was asked to record the ECG and make measurements of ECG intervals because it was known that quinidine lengthened the QT interval. Fortunately, the ability to record ECG signals on magnetic tape rather than on paper had just become possible. However the enormous amount of data collected eventually forced me to take courses in computer programming. This is the point when I realized that I could not learn about the effects of drugs just by drawing graphs. I needed to use quantitative models to describe the time course of ECG changes as a function of quinidine concentration.

Lewis Sheiner was the primary supervisor for my fellowship but it was only after several years of work collecting data that he introduced me to modeling and parameter estimation. After months trying to make sense of quinidine pharmacodynamics I taught myself enough about computers and programming to develop a pharmacokinetics–pharmacodynamics (PKPD) modeling program (MKMODEL) based on the NIH-supported PROPHET system.

When my fellowship was finished, I was offered a junior faculty position at UCSF and started to help other fellows and PhD students who were working mainly on pharmacokinetic (PK) problems but occasionally there was some connection to drug effects (2,3) and even binding to drug receptors (4).

Based on my accumulating experience of PK and PKPD problems I was encouraged by Lewis Sheiner to write a

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Fig. 1. Acetyl choline concentration–effect relationship. Contractions of a segment of guinea pig ileum suspended in oxygenated warm Krebs solution are recorded after addition of known doses of acetyl choline to a fixed volume so that the concentration could be calculated. Contractions were recorded by a mechanical lever system which scraped charcoal from the surface of a smoked rotating drum

review of PKPD ideas. In fact we wrote three very similar reviews (5–7) over a short period of time. The material in each review was more or less the same but the review for *Clinical Pharmacokinetics* had more figures and simpler mathematical expressions which may explain why that review was cited much more than the others.

The aphorism “Pharmacokinetics is what the body does to the drug—pharmacodynamics is what the drug does to the body” was mentioned in one of the reviews I wrote with Lewis Sheiner (5) but I have no idea where we heard it. Benet believes he used it in a workshop in 1980 which was eventually published in a book in 1984 (8). However, there is an earlier publication by Wolfgang Rischel (9) with these words “In Pharmacokinetics we ask: What happens to the drug in the organism after its liberation from the dosage form? And in Pharmacodynamics we ask: What happens to the organism under the influence of the drug?” (translated for me by Professor Rischel). While these words are similar, they are not as close as the words in Swedish attributed to Björn Erik Roos who was a lecturer in clinical pharmacology in Gothenberg in the early 1970s (Hartvig P, personal communication, 2009). The origin of the aphorism is still undocumented but it has been very useful in helping to

understand the difference between pharmacokinetics and pharmacodynamics. Around the time these reviews were written, the term pharmacokinetics was still being used to include not only the time course of drug concentrations but also drug effects. Les Benet cited his use of the term “pharmacokinetics” on October 2, 1980 at the First North American Conference on the Effects of Disease States on Clinical Pharmacokinetics in Vancouver, BC “Pharmacokinetics is the study of the kinetics of absorption, distribution, metabolism and excretion of drugs, and their corresponding pharmacologic, therapeutic and toxic response in man and animals.” (Benet LZ, personal communication, 2008).

Lewis Sheiner will be remembered for many contributions to clinical pharmacology and the science of pharmacometrics. One of his most outstanding papers linking concentration and effect was among his first publications. He described a turnover model for clotting factors and how the time course of prothrombin time could be predicted from warfarin concentration (10). This paper not only provided a linked physiological and pharmacological explanation for delays in drug effect but also evaluated the cost and effectiveness of a computer program to predict future doses. His next pharmacodynamic publication, 7 years later, was much more empirical. Procainamide salivary concentrations were being evaluated as an alternative to blood concentrations and it was noticed that changes in the QT interval were more closely linked in time to saliva compared with blood concentrations (11). Another 3 years passed before his description of the effect compartment model using studies of d-tubocurarine performed by Don Stanski (12). This general method for describing delayed drug effects was the state-of-the-art of PKPD modeling at the time of our review, and Don Stanski, who was a clinical pharmacology fellow with Lewis Sheiner, went on to use it to describe the pharmacodynamics of many drugs used in anesthesia. It was only later that Sheiner discovered the effect compartment idea had been described 1-year previously by Segre (13).

In the 20 years since the publication of the “Understanding” review the idea of using PK to explain the time course of effects has become widely used. But having a data-driven PK model is not really necessary. Just the idea of a PK-driven input can be helpful to describe drug responses. I was able to use the idea of an effect compartment model to show that the effects of tacrine in Alzheimer's disease were delayed much longer than one would predict from PK studies (14). The same idea was subsequently extended to the effects of levodopa in Parkinson's disease and was essential in distinguishing the slow onset symptomatic effects from persistent disease modifying effects (15). The combination of PKPD models with models for disease progression now provides a framework for understanding prolongation of survival and delaying other clinical events. This is the next frontier to be explored by clinical pharmacologists with the goal of understanding the actions of drugs and how to improve human health.

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