PERSPECTIVES IN PHARMACOKINETICS

Pharmacokinetic/Pharmacodynamic Modeling: What It Is!

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Although Pharmacokinetic/pharmacodynamic modeling has been around for decades, it is still in its infancy with respect to the future of its current manifestation. Due to the amount of time and other resources that must be committed for successful development and application of these methods, economic incentives must be made available to academic and industrial scientists through the NIH and FDA, respectively. The long-term returns should more than compensate for the investments in the form of scientific understanding of the concentration-effect relationships as well as more efficient and acceptable NDAs. Could this be the answer to the drug lag in the United States and other countries?

KEY WORDS: pharmacokinetic modeling; pharmacodynamic modeling; receptor onset/offset rate; nonparametric models; predictive modeling.

INTRODUCTION

Pharmacokinetic (PK) and pharmacodynamic (PD) modeling—What is it? What is its history? What is its current status? What is its future? I will give you my perspective on these questions as well as the hows and whys that go with them in the course of this article. However, before we move into the realm of PK/PD modeling, let us discuss the reason for the existence of any model. Models can be used for data reduction and interpolation, but their major value is derived from extrapolation beyond the existing data, e.g., from single to multiple doses, from intravenous (iv) to oral (po) dosing, etc. For models to be useful in extrapolation, they need to be valid—at least for the purpose of the extrapolation. In compartmental
modeling, complete or at least partial identifiability is required for extrapolation beyond the observed data. For example, if a two-compartment model is required to describe plasma data, structural identification of one of three potential two-compartment models is necessary to use the model to predict peripheral compartment concentrations or urinary excretion data. Identifiability becomes important later in our discussions. Now that we have the general basis of modeling in perspective, let us move on to the specifics of PK/PD modeling.

**WHAT IS IT?**

It is the basis for therapeutic drug monitoring. It is the basis of pharmacokinetics. We believe that the concentrations of drug at the site(s)-of-action influence the pharmacologic effect and that plasma or urine concentrations reflect the site-of-action concentration although only temporarily in some cases. Therefore, we measure biofluid concentrations assuming that they will give us some insight into the pharmacologic effects we ultimately see. If we do not believe this premise, then why do we measure drug concentration in the body of animals and humans? Yet our literature abounds with commentary like “There appears to be no correlation between the plasma concentrations of the benzodiazepines and their observed effects” (1-3); or with reference to the bioequivalency issue, “For many psychotropic drugs, no correlations have been found between either therapeutic effects or side effects and peripheral blood levels” (4). Perhaps we should be looking somewhat harder.

It is an empirical method to correlate direct and/or indirect effects of a drug with the biofluid drug concentration-time profile. It can be simple if the effect of the drug is direct and the site-of-action is in fast equilibrium with the sampled biofluid and the mechanism (biochemical or receptor mediated) of action is fast. It can be extremely complex if one or more of these criteria are not met. More important, the complex scenarios leave several alternative models available to describe one set of data. There are many potential steps between biofluid drug concentration and observed effect; e.g., distribution to the site-of-action, receptor association and dissociation kinetics, and/or indirect effects. Oversimplification of steps between the two events has led and may continue to lead us astray. This point is also discussed later.

**WHAT IS ITS HISTORY?**

The history of PK/PD modeling has been an evolutionary one. Based on the underlying premise that drug must be delivered to the site-of-action