Translating Pharmacokinetic and Pharmacodynamic Data into Practice

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KEYWORDS

• Pharmacokinetic • Pharmacodynamic • Study design • Drug movement

KEY POINTS

- Pharmacokinetics includes the study of bodily absorption, distribution, metabolism, and excretion of drugs via mathematical modeling.
- Volume of distribution, clearance, and elimination half-life are 3 dose-independent pharmacokinetic parameters that can be used for interspecies comparison.
- Pharmacodynamics is the study of the effects of a drug on the body and depends on the dose-response curve.
- Clinically relevant parameters include bioavailability, maximum concentration, time to maximum concentration, and half-life.
- The presence of plasma drug concentrations does not automatically correlate to a pharmacodynamic response.

INTRODUCTION

A variety of studies can aid the clinician in selecting drug doses and appropriate dosing intervals. A combination of pharmacokinetic (PK) and pharmacodynamic (PD) studies can be used to formulate an effective dose within a species. PKs can be defined as the modeling of the time course of a drug in the body.[1] These studies seek to generate mathematical models to quantify physiologic processes in the body, tailoring a dose for a given population and optimizing therapeutic effectiveness while minimizing toxicity. A PK study measures the concentration of a given drug or its metabolites in blood, tissue, feces, or urine over a set period of time.[2] The most common and accessible site is blood, leading to most PK studies reporting this compartment. However, presence of drug within the plasma does not equate to therapeutic drug concentrations at the targeted site. For example, if the target is the brain, inferences can be made regarding the ability of a drug to cross the blood-brain barrier;

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however, unless the concentration within the brain tissue is measured, there is no 100% certainty. Also, if a drug is given orally to treat a pyoderma, efficacy cannot be guaranteed unless the drug concentration is quantified in the skin.[3] Establishing therapeutic efficacy of a drug warrants the use of PD studies, which evaluate the effect of the drug on the body at a given dose, including effects at the molecular level, the clinical response, and potential adverse events (AEs). Using the measured plasma (or serum) drug concentration (PDC), mathematical modeling can be used to calculate PK parameters and, when integrated with PD, provides the dose-response relationship. This relationship is best described as

$$\textit{Dose} = \frac{\textit{Cl} \times \textit{ED}_{50}}{\textit{F}} \quad (1)$$

In which *Cl* is overall clearance, ED_{50} is the therapeutic effective PDC in 50% of the population, and *F* is the bioavailability of the drug given by a specific route.[2,3] Both PK and PD studies depend on the PDC; the former to calculate parameters for dosing and dosing interval, the latter to determine a therapeutically effective dose and minimize the risk of toxicity.

BUILDING CONFIDENCE IN INTERPRETING PHARMACOKINETIC OR PHARMACODYNAMIC PAPERS

Before examining the results of a PK or PD study, the study design should be critically evaluated. There are 5 central questions that the clinician should always ask and be able to answer, using a journal article to build confidence.

What Was the Number, Gender, and Age of Animals Used in the Study?

Because PK and PD studies are based on a calculation of averages, a higher number of animals ensures that the individual variation in overall clearance and drug metabolism will have less impact on the final parameters. On average, most exotic PK studies involve a limited number of animals and only a limited number of samples can be collected due to their size. By having a large population size, the influence of a single individual does not skew the results. It is also vital to include gender whenever possible because there are reported gender differences in the rate of metabolism in some species.[4] Species with reported gender PK differences include paroxetine in parrots[5] and meloxicam in ferrets.[4] However, these studies included a very small number of animals and the clinical impact of these differences has yet to be determined. The same challenges occur when considering age. Young animals have less fat and more water compared with healthy adult animals. As the animal ages, there is a loss of lean body mass, a decrease in renal function, and an increase in fat. Therefore, drugs with significant renal excretion (eg, aminoglycosides) require a prolonged dosing interval and drugs with significant fat distribution (eg, diazepam, hormones) will have lower PDC and prolonged elimination half-lives.[6] PK comparisons between different age groups are limited, and the use of therapeutic drug monitoring (TDM) is recommended.

Is the Study Designed as a Cross-Over, Parallel, or Single-Route Study?

In a cross-over study, the same animals are given 2 or more formulations, routes, or doses of a drug (eg, intravenous [IV] vs oral meloxicam).[7] This removes individual variability when comparing parameters such as area under the curve and bioavailability. In a parallel study, animals are divided into groups depending on the number of routes being tested but each will have only a single route or dose tested, thereby increasing