What is Toxicokinetics (TK)?

Toxicokinetics (TK) is defined as the generation of pharmacokinetic (PK) data, either as an integral component in the conduct of non-clinical toxicity studies or in specifically designed supportive studies to assess systemic exposure.

TK describes the use of bioanalytical sampling to characterize the disposition of a target compound during time-course toxicity studies in animals. TK is closely related to PK, which is defined as the process of drug absorption, distribution, metabolism, and excretion (ADME) in a living organism. All drugs under development to treat human diseases must undergo a series of PK/TK investigations in animals and humans to gain an understanding of their properties.

The primary objective of toxicokinetics is to describe the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study. TK is largely reflective of the ADME of a molecule as it moves through the body of an organism. As with all animal studies, interspecies differences in ADME should be considered prior to clinical human testing and during data extrapolation. If correctly utilized, TK studies can provide quantifiable endpoints to better explain negative effects that may arise during toxicity studies. Furthermore, recent advances in sampling technologies have made TK studies more efficient.

Toxicokinetics versus Pharmacokinetics

While TK shares important parameters, like Cmax and AUC, with preclinical PK, the studies are distinct in several ways:

- **The primary goal of TK is to correlate findings of toxicity (not therapeutic efficacy) with a corresponding level of exposure to an experimental drug compound.**
- **TK studies often use doses that are much higher than would be considered therapeutically relevant. Administration of these higher doses can potentially yield distinct kinetics from those of PK studies, which might inform dosing considerations and drug safety margins in later stages of drug development, both nonclinical and clinical.**
- **The TK arm of a nonclinical toxicology study generally has fewer timepoints, fewer subjects and fewer endpoints compared to nonclinical and clinical PK studies.**
- **Half-life (t½) may not be accurately determined in TK studies (although it is frequently estimated) due to relatively sparse sampling of blood or plasma for concentration-time analysis.**

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How Does ADME Influence Toxicokinetics?

In animals, as well as in humans, xenobiotics, or foreign chemical compounds, can undergo drastic changes in location and chemical composition during their passage through the body. In preclinical studies, sponsors hope to derive as much relevant information on their compound as possible.

ADME directly impacts TK studies quantitatively, by affecting concentration versus time-dependent parameters, and qualitatively, through producing therapeutic effect and/or toxicity on a molecular level. Understanding the implications of ADME on TK can help sponsors start to piece together the biochemical puzzle.

**ABSORPTION**

Absorption is the process of a drug being absorbed by the body’s tissues. In TK studies, the route of administration can affect how rapidly and where in the body a drug is absorbed. For example, drugs that are administered orally may take some time to be absorbed by the digestive tract and cross the gut-blood barrier into the systemic circulation. Drugs administered intravenously, however, move into the bloodstream immediately.

Route of administration and drug formulation, which impacts the rate of dissolution of a drug compound, can drastically affect a related pharmacological parameter: bioavailability. Bioavailability is defined as the fraction of an administered dose that reaches the systemic circulation and can induce pharmacological effect. In order to gain a more accurate picture of how a drug will be absorbed in later stages of development, choosing the best route and a formulation that closely mimics the intended clinical formulation (and sticking with it) can save time and resources.

**DISTRIBUTION**

Distribution describes where the drug goes once it arrives in the bloodstream and involves similar considerations to absorption. In TK, distribution can be thought of as the reversible transfer of a molecule from the blood into other compartments, or the distinct body fluids that comprise an organism. The fraction of the total dose of drug in the body to the concentration of drug in the blood plasma at any given time yields a quantifiable, though theoretical, pharmacokinetic parameter: volume of distribution.

**METABOLISM**

Metabolism defines how the chemical composition of the drug changes while moving through the body. In drug metabolism, we are particularly concerned with specific categories of enzymes that modify or add functional groups to the original drug molecule. In TK, it is especially important to consider the ramifications of these chemical changes, as some compounds may still be active after one or multiple rounds of metabolism.

Also of importance is the abundance of the expected metabolizing enzymes in a TK experiment, as this can vary depending on species, sex, tissue type, and age. In choosing an appropriate animal model for your study, consider whether the animal produces similar metabolites as humans in response to drug administration. If humans produce unique or disproportionately higher amounts of some metabolites, your TK strategy may need to be refined.

**EXCRETION**

Excretion is the process of an active drug compound and its metabolites leaving the body. Each of the previously mentioned parameters can impact the rate and route of excretion. Rate of excretion matters for overall exposure during a TK study; slow excretion can amplify toxic effects, yet rapid excretion may indicate a lack of distribution to target tissues.

In animal TK studies, like in humans, polar drug compounds may be voided intact by the kidneys through the urine. The liver can modify parent drug compounds further, contributing to excretion through bile and urine. Sampling and analyzing these materials can provide beneficial information on the percentage of the drug excreted through one route versus the other and the identity of metabolites relevant to each route.
Microsampling in Toxicokinetics

Over the past decade, advances in microsampling technologies and the development of more sensitive analytical techniques have greatly improved the efficiency of TK studies. Microsampling is a technique that captures blood draws of 10–50 microliters (µL), depending on the sensitivity of the bioanalytical method, from experimental animals at regular intervals following drug dosing. These advances have generated several benefits for the field of TK, including:

- Smaller collection volumes mitigate the detrimental effects of hemostasis, reducing the impact to relevant toxicological findings.
- With less impacts from hemostasis on the main toxicity study animals, the need for TK satellite studies (studies conducted separately from general toxicity studies) is reduced, saving resources.
- Rather than comparing satellite groups with main toxicity study animals, toxicity findings in an individual animal can be directly associated with TK in that animal.
- TK studies can be conducted with increased granularity, resulting in more precise endpoints.

In an updated guidance from 2018 (S3A Guidance), FDA underscored the overarching advantages of using microsampling, as it aligns with the field’s commitment to Reduction, Replacement and Refinement (the 3Rs) by decreasing the need for extra animals and larger blood samples. Your program may benefit from the cost savings of not running unnecessary studies.

Conclusions

In conclusion, TK studies share many common parameters with PK studies, but the purpose of these study types and their relevant dose levels are different. Specifically, TK studies serve an integral role in preclinical drug development because they relate exposure (AUC and Cmax) to toxic effects from high doses of an experimental drug. TK studies can also be performed more efficiently than ever before through recent advances in microsampling techniques.

Visit our toxicokinetic services page to learn more about our capabilities, and find out how Nuventra’s nonclinical drug development experts can help you with designing and conducting TK studies.