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Application of Pharmacokinetic Modeling Approach in Development of Therapeutic Macromolecules

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Recent great advances in genome-inspired high-throughput target discovery have stimulated the development of a myriad of mechanism-based therapeutic agents, ranging from small-molecule kinase inhibitors to therapeutic proteins and peptides. Similar to the conventional small molecular synthetic drugs the major determinant of the utility and efficacy of a biological macromolecule is its pharmacokinetics (PK). The term 'pharmacokinetics' was coined by Dost in 1953 to describe "the science of quantitative analysis between organism and drug" [1]. As a comparatively new scientific discipline with many of its concepts and approaches borrowed from other fields, such as engineering, applied mathematics and statistics, PK has undergone considerable development since the first English language review of the subject published in 1961 [2], and gained increasing prominence as a powerful tool to aid in drug discovery and development as well as the optimization of dosage regimen in patients with different disease states. PK, sometimes defined as a study of the fate of drugs in the body, is concerned with the time course of the absorption, distribution, metabolism and excretion (ADME) of a drug in a biological system. The key feature of PK is to utilize mathematical equations to describe drug concentration-time profiles and derive primary PK parameters, such as volume of distribution, half-life and clearance. The far most commonly used PK approaches are based on classical compartmental and physiological models.

Compartmental models, also referred to as the mammillary plasma clearance models, are the most commonly used PK models, in which the body is simplified to a system of connected compartments with drug transferred to and from a central compartment. The application of classical compartmental models has come of age in the non-clinical and clinical evaluation of small molecule drugs. However, the PK characterization of macromolecular drugs often presents some unique prospects and challenges. For example, the determination of exogenous therapeutic proteins and peptides is frequently complicated by the presence of an endogenous mixture of closely related or even identical substances. One approach to address this issue is to incorporate the native protein or peptide levels into the PK model so as to estimate PK parameters based on the sum of endogenous and exogenous substance concentrations detected after the exogenous administration of the substance. In a study by the Jusko group, the investigators administered glucagon-like peptide 1 (GLP-1) to healthy Sprague-Dawley rats after glucose challenge [3]. PK models developed to characterize the time course of GLP-1 blood concentrations after dosing by four different routes, i.e. intravenous bolus, intravenous infusion, subcutaneous bolus and intraperitoneal bolus. The disposition kinetics of GLP-1 was described by a two-compartment model with linear elimination and a zero-order input accounting for endogenous GLP-1 synthesis rate. Moreover, for subcutaneous and intraperitoneal dosing, a sequential absorption model with the zero-order absorption component accounting for the initial quick rise in concentrations followed by the first-order absorption governing the slow terminal phase was proposed based on the observed initial fast absorption process and flip-flop kinetics. This empirical sequential absorption model has been applied to describe the absorption kinetics of other therapeutic macromolecules by the same research group, who observed that the flip-flop absorption kinetics and incomplete availability were fairly common with the subcutaneous dosing of macromolecules [4,5].

Although compartmental models can be used to perform simulations or extrapolate to other exposure conditions for which concentration-time data are not available, the parameters derived from such models do not have any physiological meaning, and thus are not related to a specific organ or physiological process. In contrast to the classical compartmental model, the physiologically-based pharmacokinetic (PBPK) models are comprised of specific compartments for tissues and organs involved in drug disposition, and all the anatomical compartments are interconnected through blood flow to the systemic circulation. Since the anatomical compartments and blood flows are described by physiologically meaningful parameters, PBPK models can be used to characterize drug transport and elimination in specific organs and to extrapolate PK data between species. A handful of studies over the past two decades have described the development of PBPK modeling approaches to characterize the pharmacokinetics of monoclonal antibodies (mAbs), which demonstrate complex disposition characteristics, including long half-lives, combined convective and diffusive transport, and target-mediated disposition. Davda et al. [6] developed a PBPK model to characterize the disposition of mAbCC49 and its single chain Fv constructs in normal and neoplastic tissues of nude mice. In this model, the occurrence of both passive diffusion and convection during the CC49 extravasation across the capillary wall between plasma and interstitial fluid was mathematically described by a two-pore model, while the binding of CC49 to the neonatal Fc receptor (FcRn) in the intracellular compartment that protects the IgG from catabolism was characterized by specific forward and reverse binding rates obtained from in vitro studies. A recent exploratory study by Shah and Betts described a comprehensive whole-body PBPK model constructed for a variety of antigen-specific or –nonspecific monoclonal antibodies in normal wild type, FcRn knockout and tumor bearing mice based on the antibody concentration measurements obtained from the literature [7]. Each non-tumor tissue compartment in the model

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was divided into three sub-compartments representing the vascular, endosomal and interstitial spaces, respectively, while the tumor compartment was further divided into vascular, endosomal and interstitial and intracellular subcompartments. Moreover, the model was able to account for the FcRn-mAb interaction, which contributed to the prolonged mAb half-life in plasma, by altering the association and dissociation rate constants between them Ab and FcRn. In both abovementioned studies, the established PBPK models were able to not only provide quantitative descriptions of the fate of a mAb in biological systems but be scaled up to predict the ADME of the mAb in humans.

In summary, given the complex dispositional characteristics and binding kinetics of biological macromolecules, it is expected that PK models used for small molecule drugs may not be appropriate for macromolecular therapeutic agents. The choice of an appropriate PK model for a therapeutic macromolecule should be justified by the increased model quality and capability to provide enhanced insight into the interplay among crucial physiological, physiochemical and biochemical determinants of the ADME processes.

References

1. Dost FH (1953) Der Blutspiegel-Kinetic der Konzentrationsablaiife in der Krieslaufflussigkeit. Thieme, Leipzig 244.
2. Nelson E (1961) Kinetics of drug absorption, distribution, metabolism, and excretion. J Pharm Sci 50: 181-192.
3. Cao Y, Gao W, Jusko WJ (2012) Pharmacokinetic/pharmacodynamic modeling of GLP-1 in healthy rats. Pharm Res 29: 1078-1086.
4. Radwanski E, Chakraborty A, Van Wart S, Huhn RD, Cutler DL, et al. (1998) Pharmacokinetics and leukocyte responses of recombinant human interleukin-10. Pharm Res 15: 1895-1901.
5. Mager DE, Jusko WJ (2002) Receptor-mediated pharmacokinetic/pharmacodynamic model of interferon-beta 1a in humans. Pharm Res 19: 1537-1543.
6. Davda JP, Jain M, Batra SK, Gwilt PR, Robinson DH (2008) A physiologically based pharmacokinetic (PBPK) model to characterize and predict the disposition of monoclonal antibody CC49 and its single chain Fv constructs. Int Immunopharmacol 8: 401-413.
7. Shah DK, Betts AM (2012) Towards a platform PBPK model to characterize the plasma and tissue disposition of monoclonal antibodies in preclinical species and human. J Pharmacokinet Pharmacodyn 39: 67-86.