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Review – Part of the Special Issue – Pharmacology in 21st Century Biomedical Research

Pharmacokinetics

Jianghong Fan, Inés A.M. de Lannoy *

InterVivo Solutions Inc., 120 Carlton Street, Suite 203, Toronto, ON, Canada M5A 4K2

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ABSTRACT

Pharmacokinetics (PK) is the study of the time course of the absorption, distribution, metabolism and excretion (ADME) of a drug, compound or new chemical entity (NCE) after its administration to the body. Following a brief introduction as to why knowledge of the PK properties of an NCE is critical to its selection as a lead candidate in a drug discovery program and/or its use as a functional research tool, the present article presents an overview of PK principles, including practical guidelines for conducting PK studies as well as the equations required for characterizing and understanding the PK of an NCE and its metabolite(s). A review of the determination of *in vivo* PK parameters by non-compartmental and compartmental methods is followed by a brief overview of allometric scaling. Compound absorption and permeability are discussed in the context of intestinal absorption and brain penetration. The volume of distribution and plasma protein and tissue binding are covered as is the clearance (systemic, hepatic, renal, biliary) of both small and large molecules. A section on metabolite kinetics describes how to estimate the PK parameters of a metabolite following administration of an NCE. Lastly, mathematical models used to describe pharmacodynamics (PD), the relationship between the NCE/compound concentration at the site of action and the resulting effect, are reviewed and linked to PK models in a section on PK/PD.

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* Corresponding author.
E-mail addresses: jianghongf@intervivo.com (J. Fan), inesd@intervivo.com, ines.delannoy@utoronto.ca (Inés A.M. de Lannoy).

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1. Introduction

While potency, efficacy and selectivity are key attributes of a new chemical entity (NCE) that drive its characterization as a compound of potential interest in the drug discovery process or as a research tool that can be used to interrogate biological systems *in vitro* and *in vivo*, unless the pharmacokinetics (PK) properties of an NCE are known, its use *in vivo* becomes limited by shortcomings in PK that can confuse data interpretation and result in experimental outcomes that are invalid. For instance, when making species comparisons of plasma exposure of an NCE *in vivo*, without knowledge of the variations in plasma protein binding and metabolic liability across species, correlation of the pharmacological response with plasma exposure becomes challenging. As Hodgson has cogently noted [1] – "A chemical cannot be a drug, no matter how active nor how specific its action, unless it is also taken appropriately into the body (absorption), distributed to the right parts of the body, metabolized in a way that does not instantly remove its activity, and eliminated in a suitable manner – a compound must get in, move about, hang around, and then get out." Thus, evaluating the properties of a compound, especially an NCE, *in vivo* without knowledge of its PK properties – even at a rudimentary level – is an exercise in futility. The present overview provides an introduction to the principles of PK, including guidelines for conducting PK studies and the equations required for characterizing and understanding the PK of an NCE and its possible metabolite(s).

2. Background

Pharmacokinetics (PK) is the study of the movement of xenobiotics (drugs/compounds/NCEs) within the body after their administration, whereas pharmacodynamics (PD) is the study of the relationship between the concentration of a compound/NCE at its site of action, where the therapeutic targets (*e.g.*, receptors, transporters or enzymes) are located, and the magnitude of the pharmacological response. In the simplest of terms, what distinguishes PK from PD is that the former describes what the body does to the compound, whereas PD describes what the compound does to the body [2]. Both fields of study are important for investigating the disposition profiles and pharmacological efficacy of compounds/NCEs in the body [3], and may be influenced by experimental as well as clinical conditions (*e.g.*, gender, species, age, disease state).

In the past, drug discovery programs often concentrated their efforts solely on selecting the most potent or efficacious compound in *in vitro* receptor binding or functional assays, respectively, that were designed to test hundreds to thousands of compounds, and failed to generate data on whether a compound would have the ability to reach its therapeutic target at a sufficient concentration and for a sufficient amount of time to alter target function when administered *in vivo*. This strategy was noted as being detrimental to developing a successful drug, with a retrospective analysis of 7 U.K. owned pharmaceutical companies conducted up to 1985 revealing that 39% of NCEs failed in the clinic due to poor PK properties [4]. Careful assessment of the PK profile in selecting and