ScienceDirect

Biochemical Pharmacology

Volume 87, Issue 1, 1 January 2014, Pages 93-120

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

Pharmacokinetics

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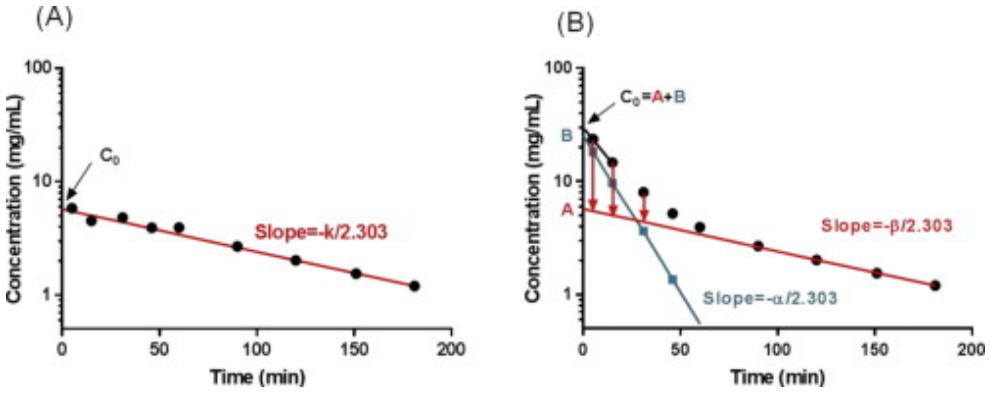
Abstract

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.

Graphical abstract



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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).

Section snippets

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 …

Overview of basic PK processes

The four fundamental processes which influence the *in vivo* PK of a compound are *absorption, distribution, metabolism* and *excretion* (ADME). These are distinct, although in many respects, interrelated processes which occur between the administration and elimination of a compound from the body. Following an oral (*p.o.*) dose of a compound, it must be absorbed across the intestinal lumen and not be susceptible to metabolism by intestinal enzymes before it appears in the portal vein circulation where …

Allometric scaling

PK scaling is the discipline of predicting human PK based on preclinical data obtained from one or more animal species. Allometric scaling is based solely upon differences in body size [25], without necessarily examining the underlying mechanism(s). Empirical observations indicate that many physiological parameters change as a function of size and the relationship can be described as [26]:$Y = a \cdot W^b$where *Y* is the physiological parameter that is being measured (*e.g.*, clearance or volume of …

Intestinal absorption and permeability

The key factors controlling oral compound absorption are the solubility/dissolution of the compound in the GI tract and the permeability of the compound across the intestinal membrane. The physicochemical properties of the compound (*e.g.*, solubility, hydrophobicity, ionization, MW) and the physicochemical and biological properties of the GI tract jointly determine the rate and extent of compound absorption and ultimately affect compound bioavailability following oral administration. …

Volume of distribution (V or V_d)

The extent of compound distribution and the amount of compound in the body necessarily affect the compound concentration in plasma. The extent of distribution of a compound is assessed by its volume of distribution (V), although V does not represent a real physiological volume. The real distribution volume of a compound is related to body water and cannot exceed the total body water (~58% of body weight in humans or 600 mL/kg in an average adult of 70 kg, 167 mL/rat depending in the strain [54]). …

Clearance (metabolism and excretion)

Elimination generally refers to the irreversible removal of a compound or its metabolite(s) from the body, primarily by two routes: metabolism and excretion. As already mentioned, compound metabolism generally involves a chemical or enzymatic conversion of the parent compound into one or more metabolites, which are readily excreted and excretion is mainly facilitated by renal or biliary clearance. Again, clearance reflects the ability of the body to eliminate the compound (CL_s) or a single …

Metabolite kinetics

The process of compound metabolism is, on occasion, a double-edged sword as it does not always lead to compound inactivation and detoxification. Some compounds may be converted to pharmacologically active metabolites, *e.g.*, the metabolites of tricyclic antidepressants [98] and imatinib [99], and/or to toxic metabolites, such as the metabolites of carbamazepine [100], methotrexate [101] and acetaminophen [102]. In these instances, understanding the PK of the relevant metabolite(s) is important …

Pharmacokinetics and pharmacodynamics

Pharmacodynamics (PD) describes the relationship between the compound concentration at the site of action and the effect produced by the compound, including its time course and the intensity of therapeutic and adverse effects [2]. The interaction of a compound with its target initiates a sequence of events which results in the pharmacological response. PD aims to quantify the compound effects through linking the compound effect and compound concentration at the site of action [127]. …

Conclusions

Using a compound – whether a known drug or an NCE – as a tool to aid in defining the role of a protein in cellular and tissue homeostasis and its potential as a drug target requires that the compound be hierarchically evaluated *in vitro* and *in vivo* [151], [152]. While the potency, efficacy and selectivity of a compound can be facilely determined *in vitro*, its use *in vivo* and/or potential as a drug candidate requires an understanding of its PK and ADME properties [153]. To test a compound, …

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