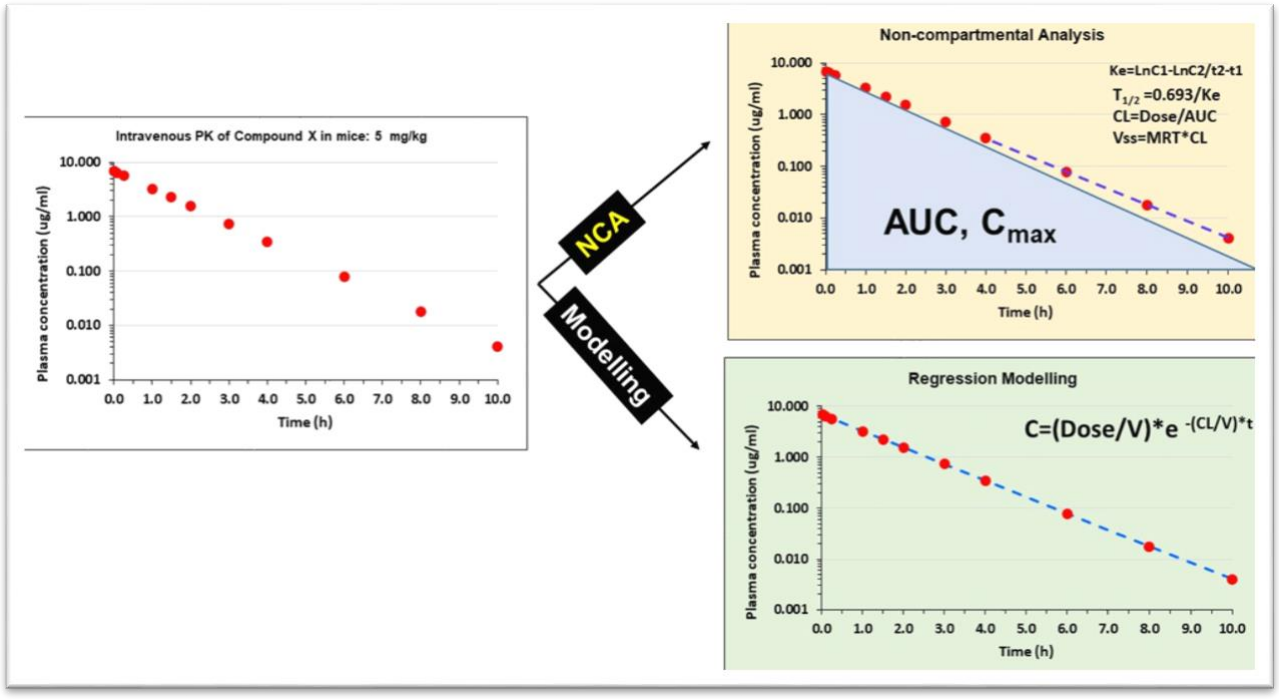
Pharmacokinetics: 1

Quantifying Pharmacokinetics

There is a causal relationship between dose, dosage regimen, exposure of drug and its therapeutic benefit and adverse effects (1).

To quantify pharmacological and toxicological effects of a drug or a molecule (e.g. Efficacy = E_{max} or I_{max}; Potency =EC_{50} or IC_{50}) based on dose and effect, it is essential to quantify its pharmacokinetics. Quantifying PK helps in understanding the relationship between pharmacokinetics (PK) and pharmacodynamics (PD) or PK/PD. Quantitative PK/PD (Quantitative Pharmacology) is the basis for setting dose, regimen and duration for treatment in nonclinical and clinical settings (2).

Methods of pharmacokinetic analysis for quantification of PK parameters:



The PK of a molecule can be analyzed and quantified using

a) Non-compartmental analysis (NCA)
b) Non-linear regression modelling

NCA: This method uses the application of the trapezoidal rule for estimating the area under a plasma-concentration time curve. This method is applicable to first-order (linear) models and does not consider compartmental behavior.

Non-linear regression modelling: This method uses mathematical equations (exponentials or differential equations) to describe the PK in terms of compartmental behaviour. The primary parameters of the model are usually based on physiologically relevant quantities such as the volume of distribution and clearance.

Application of NCA and Regression modelling in drug discovery and development for quantification of pharmacokinetics

Non-compartmental Analysis (NCA)	Regression Modelling
No assumptions of compartment behavior	Based on compartment behavior
Statistical moment analysis	Mathematical equations used to descr PK
Relevant PK Parameters: Elimination rate constant (K_e), elimination half-life ($t_{1/2}$), systemic clearance, volume of distribution, Area under the plasma concentration time curve (AUC), Peak concentration (C_{max})	Primary parameters: Volume (V) and Clearance (CL). AUC, C_{max}, $t_{1/2}$: secc parameters.
Dose proportionality analysis	Allows modelling non-linear PK
Exposure-Response analysis of efficacy, toxicity	Modelling metabolite PK
In vitro-in vivo correlations (IVIVC) in Lead identification-optimization phase	Used for simulations of different dose regimens to analyze what if scenarios late LI stage
PK/PD indices	Can be linked to PD models for PK/P evaluations in lead optimization
Allometric scaling for prediction of V, CL in humans	Predictions of PK in other species anc humans
Assessment of Drug-Drug Interactions (DDI)	Used as structural models in populatic modelling
Cannot be used for simulations of PK	Empirical, non-mechanistic
Easy to use and rapid	Time consuming compared to NCA

References:

1. Rowland, M and Tozer, T.N. Clinical Pharmacokinetics: concepts and applications. 3rd ed.
2. Gabrielsson, J.; Green, A.R.; Quantitative pharmacology or pharmacokinetic pharmacodynamic integration should be a vital component in integrative pharmacology. *J Pharmacol Exp Ther.*, 2009, 331(3), 767-74.
3. Gabrielsson J and Weiner D. 2000. Pharmacokinetic and Pharmacodynamic data analysis: Concepts and Applications. 3rd Edition. Swedish Pharmaceutical Press.

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