PP22

From Molecules to Effects: Exploring Pharmacokinetics with a Clinical Pharmacology Data Scientist

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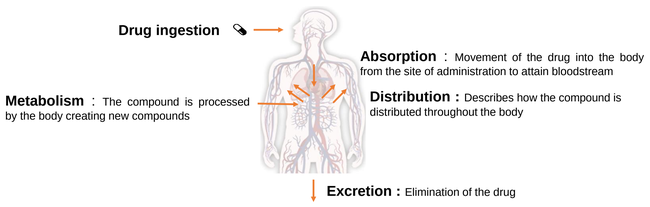
What is Pharmacokinetics ?

Pharmacokinetics (PK) analysis plays a crucial role in the drug development process, guiding in the assessment of a compound's safety and effectiveness for its intended purpose. When demonstrating the efficacy and safety of a compound in early trials, preclinical and clinical research, a drug developer can submit an application for the drug's marketing approval to official health agencies (FDA, EMEA..). These ones would rely on PK studies to decide to approve or not approve it.

To understand the fate of the drug in the body PK studies focus on the drug's concentration in the bloodstream, specifically in the plasma. This concentration is usually assed by collecting blood samples from subjects at regular intervals after drug administration and measuring the drug's concentration in these samples.

The Pharmacokinetics process : ADME



Two methods for analyzing pharmacokinetics and the properties mentioned above are : **Non-Compartmental Analysis** (NCA) and **Compartmental Analysis** (Modeling).

NCA calculates pharmacokinetic parameters using drug concentration-time data, while Compartmental Analysis modeling uses mathematical models to characterize drug behavior in the body.

This poster aims to introduce the basics of those approaches, which offer critical insights into drug behavior, indispensable in the development of safe and effective drugs.

What is a Clinical Pharmacology Data Scientist ?

Primary responsibilities of the CPDS

- Generating datasets from various **Clinical Data sources** using **CDISC** standards :
  - **SDTM data** broken into multiple domains such as PK concentrations (PC), or exposure (EX) domains
  - **ADaM data** derived from SDTM and created to enable statistical and scientific analysis
- Conducting data exploration
- Creating easily comprehensible graphics to incorporate critical information
- Conducting simulations and generating output data for reports
- Automating the workflow enabling to speed up datasets and outputs production processes

CPDS work along with Pharmacometricians, Disease Modelers and Clinical Pharmacologists by providing Data science support and ensuring data traceability and reproducibility

References & Contact

1. Buchheit, V. and Frey, N., Added value of the Data Scientist role in a Clinical Pharmacometric group, 2016 [https://www.page-meeting.org/default.asp?abstract=5884]
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Non-Compartmental Analysis

Non-compartmental analysis (NCA) methods are model-independent : they do not rely on assumptions about the body compartments.

- **NCA uses algebraic equations** to estimate pharmacokinetic parameters, making the analysis less complex compared to compartmental methods
- This approach **depends on observations** and requires rich concentration-time data
- During the initial stages of clinical pharmacology studies, NCA is typically carried out
- This method is **quicker to perform and less expensive** compared to more complex compartmental analyses

NCA also leads to a rapid determination of some PK parameters based on measurements taken following drug administrations.

Compartmental Analysis (Modeling)

Compartmental models are used to describe drug concentration and aim to find the model that best fits the data observed.

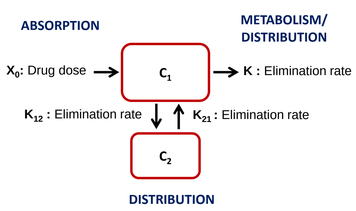
These methods consider the body as made up of a finite number of interconnected compartments (blood, organs and other tissues).

Two Compartment Model (TCM)

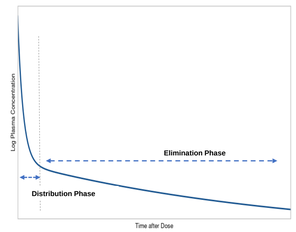
The model with two compartments is slightly more complex than the one compartmental model and the **body is conceptualized with two physiological parts.** The **central compartment C_1 consists of plasma and organs heavily supplied with blood** and the **peripheral compartment C_2 is made of tissues or parts of body less supplied with blood**.

In this model, the drug is administrated rapidly and distributed through the central compartment, then goes more slowly to the peripheral one. These two compartments are linked with each other and back and forth movements between the two compartments are observed.

Diagram of the Two-Compartmental model



Drug concentration overtime of the TCM



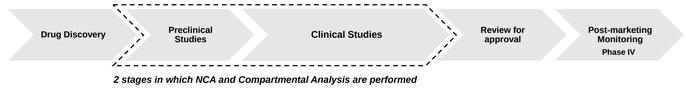
Benefits of Modeling and Simulation

- **Reducing costs**
- **Saving time**
- **Reducing animal studies**
- **Testing hypothesis and scenarios not tested during the course of clinical studies :** simulate the outcomes of dose selection, dosing interval and dosing regimen to help predict the right dose while maximizing benefits of the drug
- **Providing means for predicting the level of variabilty** that exists among individuals, using Population Pharmacokinetics models

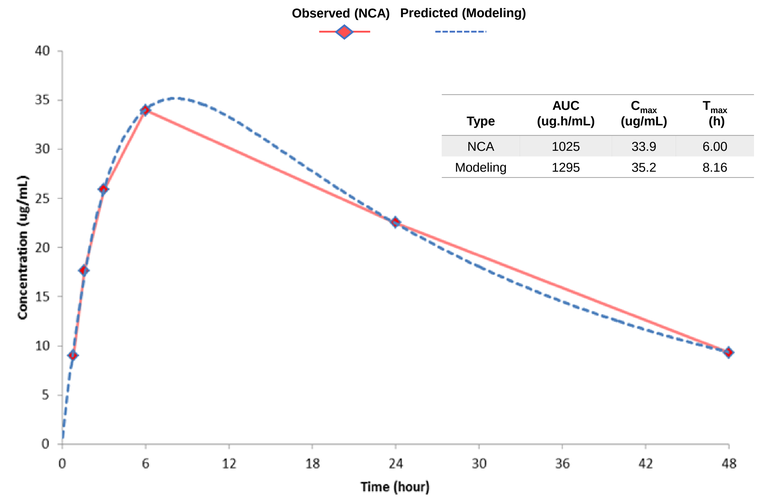
Using such approaches, allows to optimize drugs' effects through suitable dosing regimen ensuring that as many patients as possible will react positively to a drug across clinical studies.

PK Analysis

Comparing the two approaches



2 stages in which NCA and Compartmental Analysis are performed



Type	AUC (ug.h/mL)	C_{max} (ug/mL)	T_{max} (h)
NCA	1025	33.9	6.00
Modeling	1295	35.2	8.16

Modeling and Simulation	Non-Compartmental Analysis
• Curve fitting of experimental data • Can take weeks/months • Allows to simulate parameters by changing model parameters	• Simple algebraic equations • "Join the dots" approach

Most common used PK parameters

- **C_{max}, T_{max}:** Peak of drug concentration and time required to reach it, time at which absorption phase ends
- **Clearance:** Characterizes elimination phase and is the volume of plasma cleared of the drug per unit time
- **Half-life:** Time required for the blood concentration of the drug to decrease by half
- **Area under the concentration curve (AUC):** Measures overall drug exposure, NCA uses a linear interpolation to calculate this parameter
- **Volume of distribution:** Apparent volume in which drug distributes, can also be interpreted as drug's propensity to remain in the plasma or distribute to tissues