

Pharmacokinetics (PK)

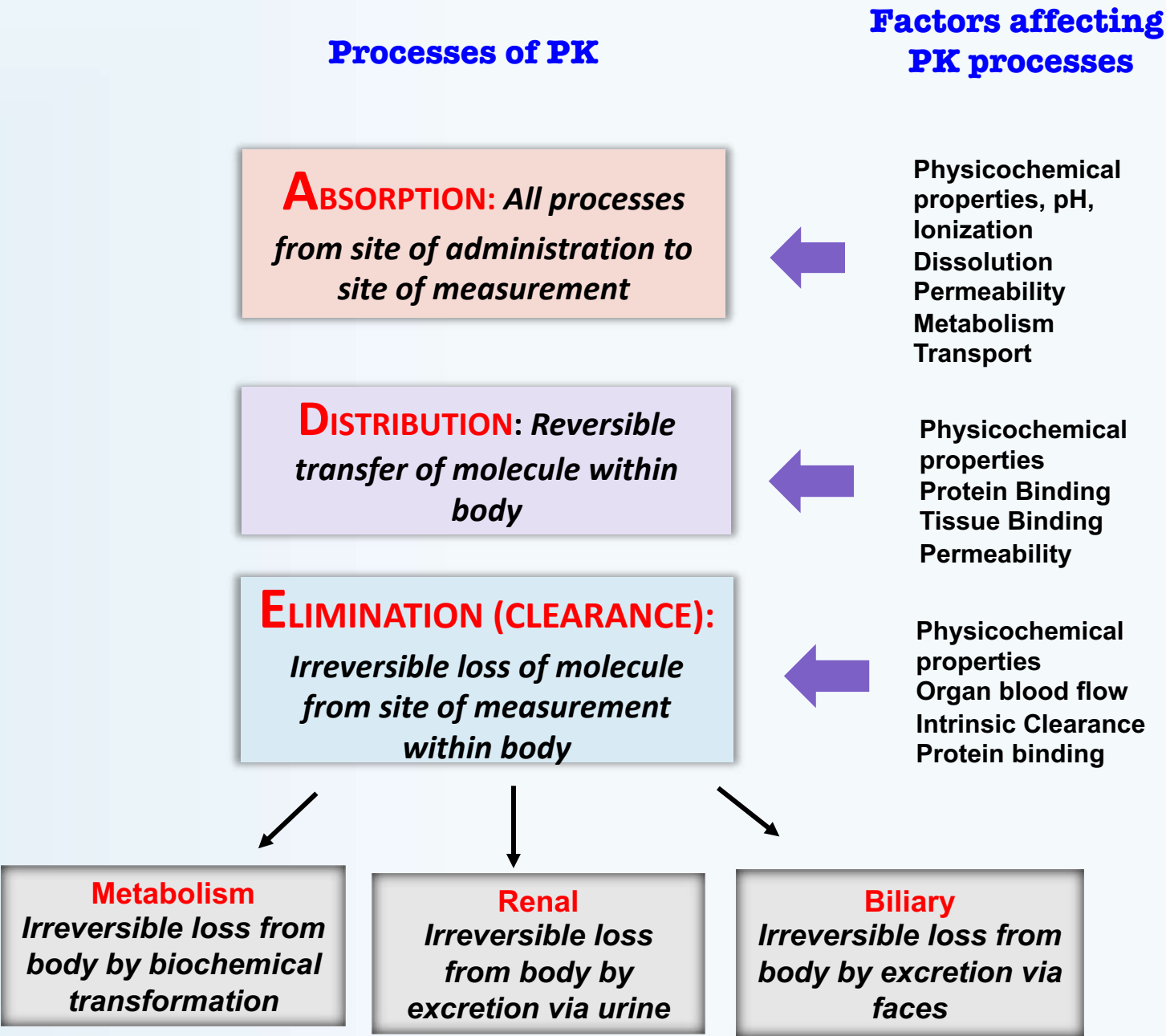
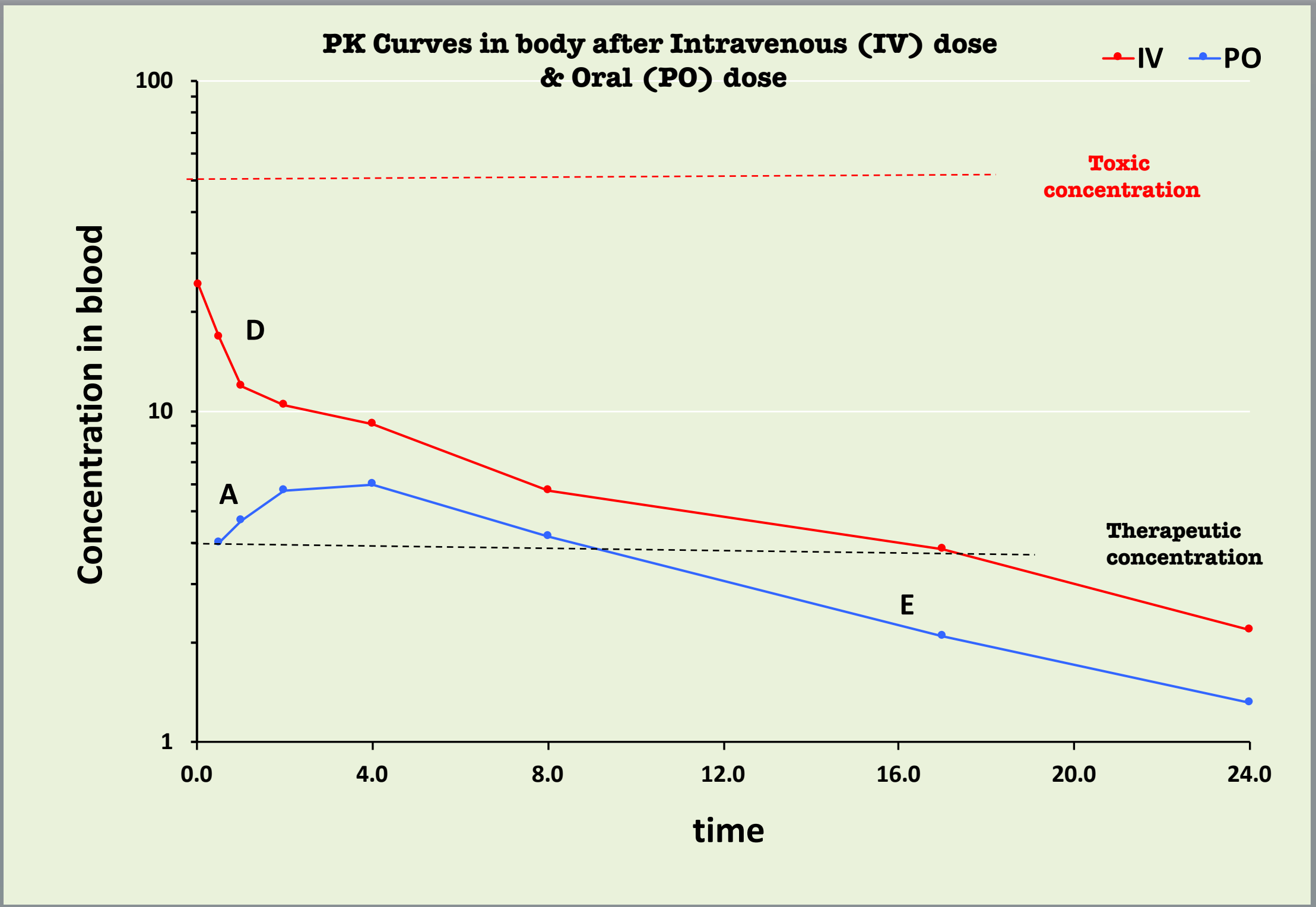
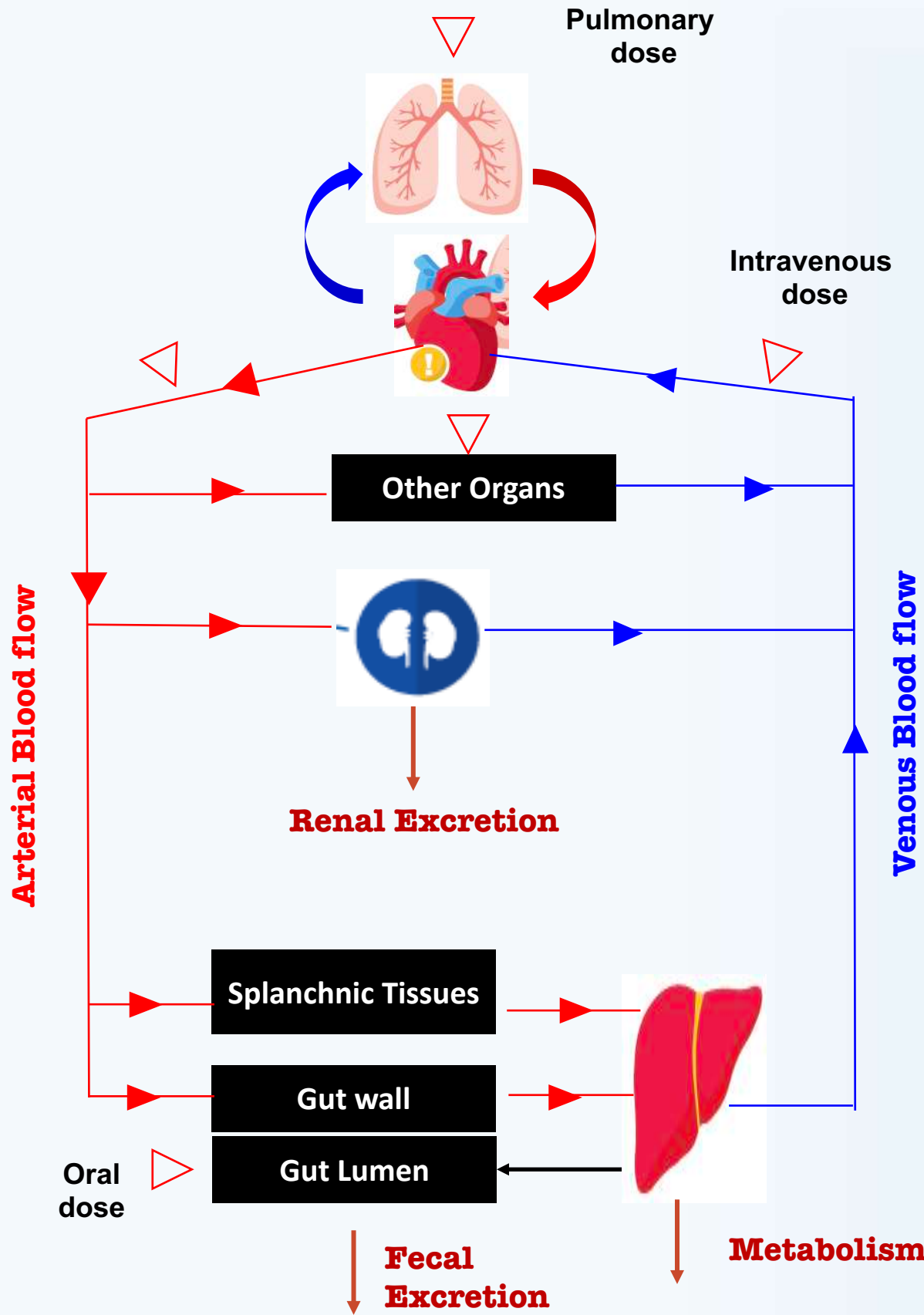
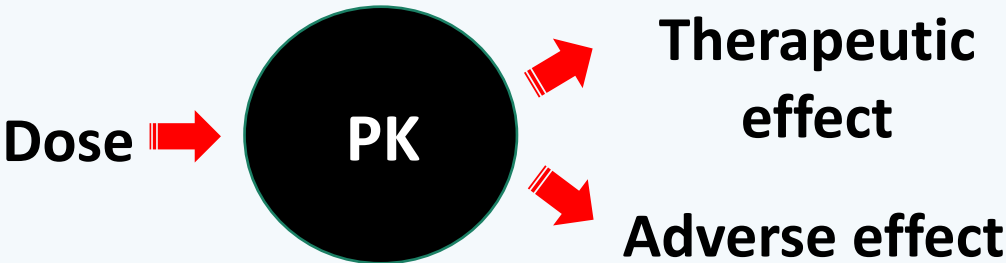
Ramesh Jayaraman

Pharmacokinetics (PK): Study of time course of concentration of drug or molecule in body.

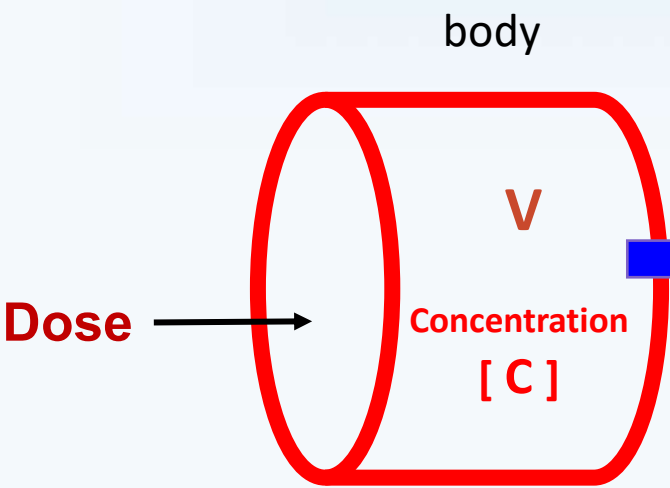
Why Pharmacokinetics: There is a causal relationship between dose, dosage regimen, exposure of drug and its therapeutic and adverse effects.

Lack of adequate PK is a major cause for failure of drug candidates in clinical development

PK knowledge helps in incorporating drug-like properties into potent molecules



Volume of distribution (V) and Clearance (CL) are fundamental parameters which determine PK profile of drug



- V**
 - Apparent volume into which drug distributes in body
 - Relates dose and concentration
 - Compared to water, blood, tissue volumes
- CL**
 - Volume of blood cleared of drug per unit time
 - Relates concentration and rate of elimination
 - Compared to liver & kidney blood flow

$$V = \frac{\text{Dose}_{iv}}{C}$$

• Knowledge of V & therapeutic C helps fix therapeutic dose
• When V constant, increasing dose will increase C proportionately

$$t_{1/2} = 0.693 \times \frac{V}{CL}$$

V & CL independently determine elimination half-life ($t_{1/2}$) of drug in body

$$CL = \frac{\text{Dose}_{iv}}{AUC}$$

• Knowledge of CL & therapeutic AUC helps fix therapeutic dose
• When CL constant, increase in dose will increase AUC proportionately

IV PK properties of drugs in mice

Drug	V _{ss} (L/kg)	CL (L/h/kg)	t _{1/2} (h)
Rifampicin	0.9	0.05	12.8
Isoniazid	0.6	0.5	0.8
Moxifloxacin	3.5	4.4	0.6
Ciprofloxacin	3.9	5.5	0.5
Ofloxacin	1.6	3.2	0.4

Applications of PK in Drug Discovery & Development

- NON-CLINICAL**
- ❑ Lead Identification & Optimization
 - ❑ Design of Pharmacology & Toxicology studies
 - ❑ Identifying Pharmacokinetic/Pharmacodynamic (PK/PD) relationships
 - ❑ Prediction of PK in humans
- CLINICAL**
- ❑ Identification of therapeutic & safe doses in clinical trials
 - ❑ Identification of doses in different human populations

References:
1. Rowland, M and Tozer, T.N. Clinical Pharmacokinetics: concepts and applications. 3rd ed
2. Gabrielsson J and Weiner D. 2000. Pharmacokinetic and Pharmacodynamic data analysis: Concepts and Applications. 3rd Edition. Swedish Pharmaceutical Press.
3. Nature Reviews | Drug Discovery. volume 20 | April 2021 | 259
4. Davies, B.; Morris, T. Physiological parameters in laboratory animals and humans. Pharm. Res., 1993 10(7), 1093-1095