Clinical Pharmacokinetics: Clearance, Volume of Distribution & Two-Compartment Models (Clinical Treatise 2015)

Por Cristiano Ricardo · Publicado em 29/04/2015

University clinical pharmacology treatise by Prof. Cristiano Ricardo on clinical pharmacokinetics: clearance, volume of distribution & two-compartment models (Clinical Pharmacokinetics & Mathematical Modeling), featuring mathematical PK/PD modeling, clinical cases, and colorful schematics.

Versão online e eventuais atualizações:
https://cristianoricardo.com/post/clinical-pharmacokinetics-clearance-volume-of-distribution-two-compartment-models-2015-04-29

Clinical Pharmacokinetics & Mathematical Modeling · Clinical Pharmacology & Pharmacotherapy

Predicting plasma drug concentrations requires rigorous integration of apparent volume of distribution, physiological clearance organs, and multi-exponential elimination.

Pharmacological Mechanism & Kinetic Schema

Distribution Phase (?-phase)
Elimination Phase (?-phase: t1/2 = 0.693 / ke)

Fundamental PK Relationships
Total Clearance (CL) = ke × Vd
Loading Dose = (Ctarget × Vd) / F

Apparent Volume of Distribution (Vd) and Tissue Binding

Vd does not represent a physical anatomical space, but the theoretical fluid volume required to account for all drug in the body at the same concentration as circulating plasma. Drugs with high tissue affinity and lipophilicity (e.g., Digoxin, Chloroquine) exhibit astronomical Vd values (> 500 L), whereas highly albumin-bound molecules (e.g., Warfarin) are restricted to the vascular space (Vd ~ 7 L).

Organ Clearance and the Extraction Ratio (E)

Clearance is the volume of biological fluid completely cleared of drug per unit time. For high-extraction-ratio drugs (E > 0.7, such as Propranolol and Lidocaine), hepatic clearance is blood-flow-limited, rendering them exquisitely sensitive to hemodynamic changes. Low-extraction drugs (E < 0.3) are capacity-limited by intrinsic enzyme activity.

Multi-Compartmental Distribution Kinetics

Following rapid intravenous bolus injection, many drugs distribute rapidly into highly perfused central organs (heart, lungs, liver, brain) before slowly equilibrating into peripheral muscular and adipose compartments, generating distinct bi-exponential plasma decay curves governed by alpha and beta hybrid rate constants.

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