Hepatic Biotransformation & CYP450 Drug-Drug Interactions (DDIs) (Clinical Treatise 2010)

Por Cristiano Ricardo · Publicado em 31/03/2010

University clinical pharmacology treatise by Prof. Cristiano Ricardo on hepatic biotransformation & cyp450 drug-drug interactions (ddis) (Xenobiotic Metabolism & Molecular Toxicology), featuring mathematical PK/PD modeling, clinical cases, and colorful schematics.

Versão online e eventuais atualizações:
https://cristianoricardo.com/post/hepatic-biotransformation-cyp450-drug-drug-interactions-ddis-2010-03-31

Xenobiotic Metabolism & Molecular Toxicology · Clinical Pharmacology & Pharmacotherapy

Enzymatic transformation by the cytochrome P450 superfamily dictates oral first-pass clearance, bioactivation of prodrugs, and severe adverse drug-drug interactions.

Pharmacological Mechanism & Kinetic Schema

Phase I Oxidation
CYP3A4, 2D6, 2C9, 2C19
Introduces -OH, -NH2
Inhibition ? Toxicity

Phase II Conjugation
UGT (Glucuronidation)
Sulfation & Glutathione
Excretable Polar Metabolite

PXR/CAR Induction
Rifampin, St. John's Wort
Transcriptional boost
Sub-therapeutic failure

Mechanisms of CYP Inhibition: Reversible vs Quasi-Irreversible

Competitive inhibition occurs instantaneously when two co-administered drugs compete for the heme catalytic pocket (e.g., Fluconazole inhibiting CYP2C9, leading to toxic Warfarin accumulation). In contrast, mechanism-based (suicide) inhibition involves covalent binding of reactive metabolic intermediates to the apoprotein (e.g., Clarithromycin inactivating CYP3A4), requiring de novo enzyme synthesis over several days for clinical recovery.

Nuclear Receptor Activation and Transcriptional Enzyme Induction

Potent inducers like Rifampin and Carbamazepine bind to nuclear Pregnane X Receptor (PXR) and Constitutive Androstane Receptor (CAR). Translocation to the nucleus heterodimerizes with Retinoid X Receptor (RXR), massively upregulating CYP3A4, CYP2C9, and P-glycoprotein (ABCB1) transcription, causing therapeutic failure of oral contraceptives and calcineurin inhibitors.

Pharmacogenomic Polymorphisms: The CYP2D6 Spectrum

Genetic copy number variations and single nucleotide polymorphisms categorise patients from Poor Metabolizers (PMs, lacking codeine analgesia due to failure of morphine bio-activation) to Ultra-Rapid Metabolizers (UMs, facing life-threatening opioid toxicity under standard codeine doses).

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