

# Hepatic Biotransformation & CYP450 Drug-Drug Interactions DDIs — Clinical Treatise 2014

Por Cristiano Ricardo · Publicado em 09/04/2014

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://cristianorichardo.com/post/hepatic-biotransformation-cyp450-drug-drug-interactions-ddis-2014-04-09>

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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, -NH<sub>2</sub>

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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