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PEARLS OF LABORATORY MEDICINE

Therapeutic Drug Monitoring—Chemotherapeutic agents

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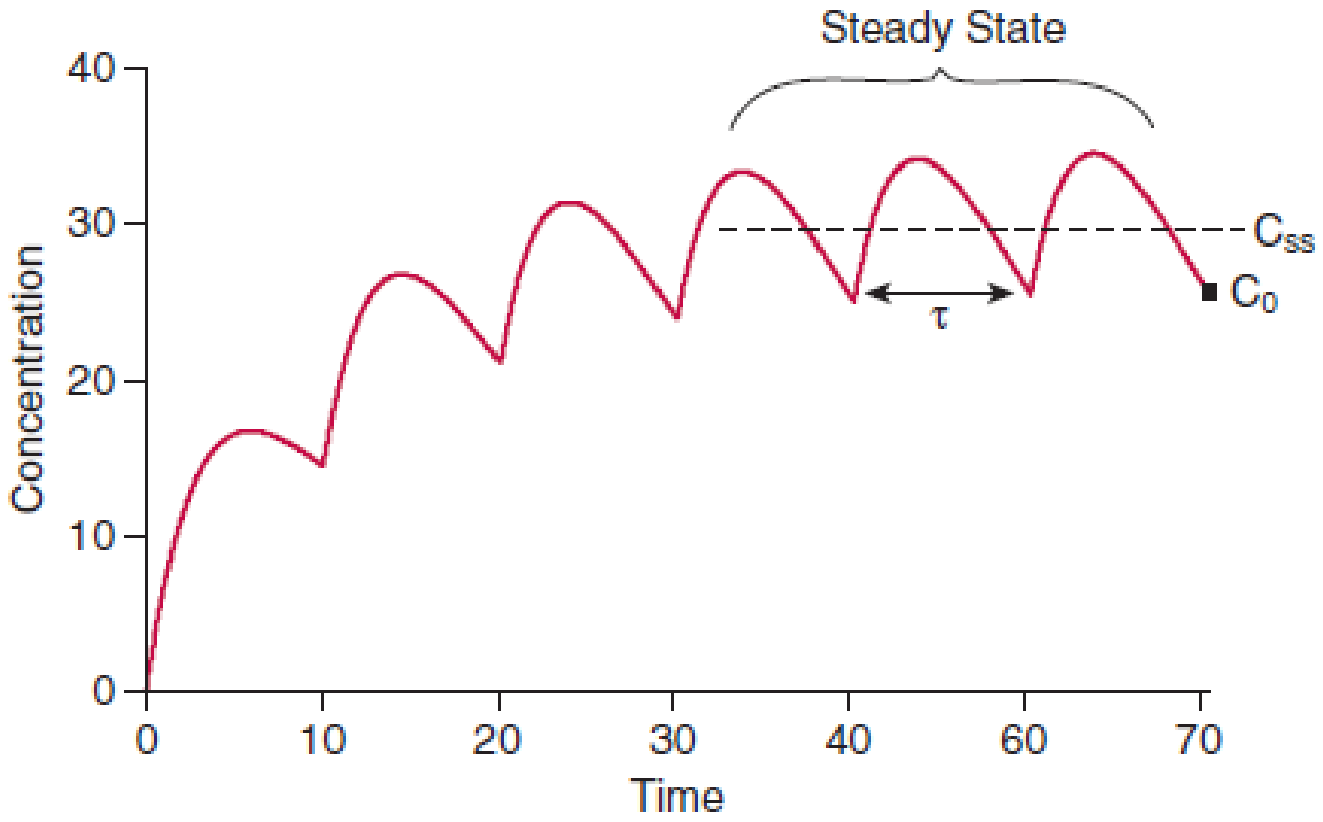
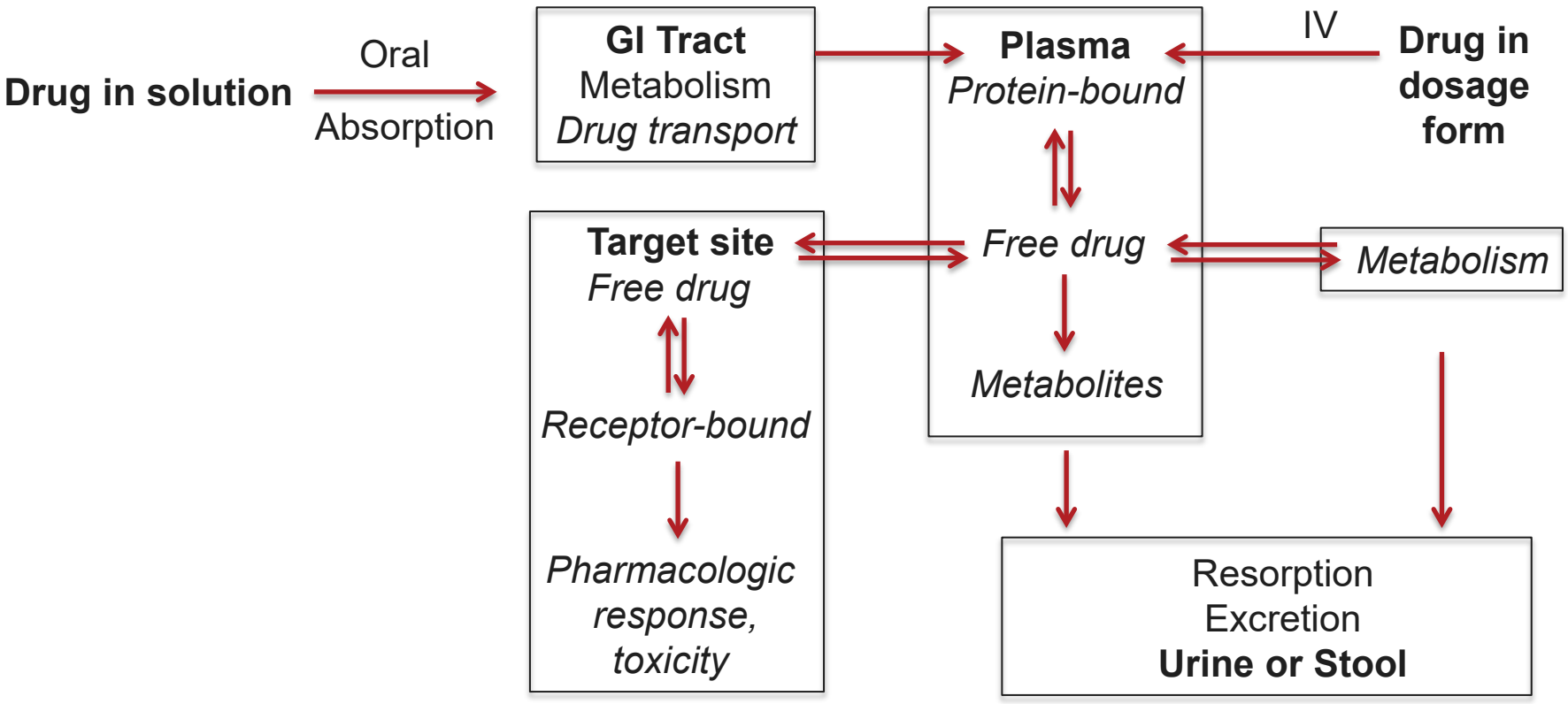
Therapeutic Drug Monitoring

- Narrow therapeutic index
- Used for long-term therapy
- Correlation between serum concentration and clinical response
- Wide interindividual or intraindividual variability in pharmacokinetics
- Absence of a biomarker associated with therapeutic outcomes
- Administered with other, potentially interacting compounds

Steady State



Pharmacokinetics



Clinical Utility

- Initial selection and dosing of a drug
- Wide interpatient variability in absorption, metabolism
- Poor response to therapeutic concentrations
- Not within the therapeutic range
- Population pharmacokinetics not adequately address comorbidities or drug interactions

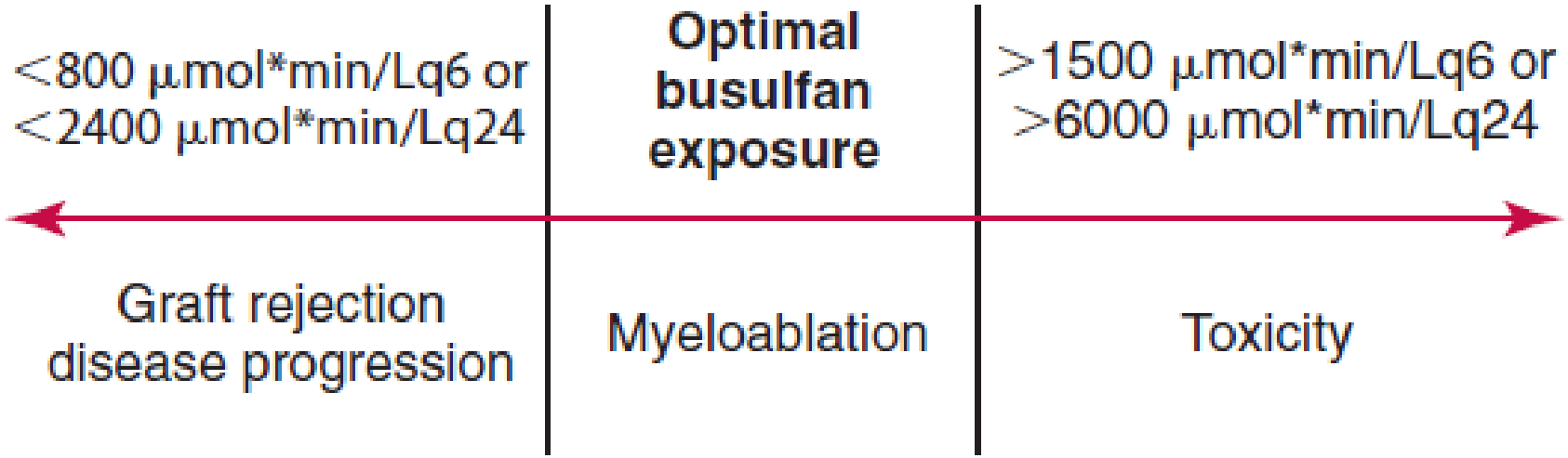
Analytical Methods

- Immunoassays
  - Enzyme multiplied immunoassay technique (EMIT)
  - Fluorescent polarization immunoassay (FPIA)
  - Cloned enzyme donor immunoassay (CEDIA)
- Chromatographic techniques
  - Gas chromatography- mass spectrometry (GC-MS)
  - Liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS)
  - High performance liquid chromatography-ultraviolet (HPLCUV)

Busulfan

- Hematopoietic stem cell transplantation
- Bone marrow disorders
  - Acute and chronic leukemias
  - Myelodysplastic syndromes
  - β-thalassemia major
  - Polycythemia vera
  - Sickle cell anemia

Busulfan Pharmacokinetics



Busulfan Metabolism

- Cytochrome P450 isoenzymes (primarily CYP3A4)
- Conjugation with glutathione via glutathione S-transferase
- Fluconazole—inhibition of CYP3A4—slow busulfan clearance

Methotrexate

- Acute lymphoblastic leukemia
- Choriocarcinoma and related trophoblastic tumors
- Carcinomas of the breast, tongue, pharynx, and testes
- Maintenance of remission in leukemia
- Severe, debilitating psoriasis
- Carcinoma of the lung and osteogenic sarcoma

Methotrexate Pharmacokinetics

Methotraxate	Minimum Effective Concentration, µmol/L	Minimum Toxic Concentration, µmol/L	Mean Half-Life, h	Mean Volume of Distribution, L/kg	Mean Protein Binding, %
At 24 hours	<10	>10	1.8	0.55	46
At 48 hours	<1	>1	8.4	0.55	46
At 72 hours	<0.1	>0.1	>10	0.55	46

Methotrexate Elimination

- Renal excretion
  - Large volume of alkaline urine

Methotrexate Toxicity

- High-dose ≥500 mg/m^2
- Leucovorin "rescue“– also called citrovorum, N-5-formyltetrahydrofolate, the product of dihydrofolate reductase
- Continuous flow hemodialysis
- Intravenous infusion of carboxypeptidase G2

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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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