Applied Pharmacokinetics in the Adult Critically Ill

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Why Study Pharmacokinetics?

- Avoid adverse drug events
  - At least 40% of adverse drug reactions are preventable
  - Almost 30% of these events involve dosing errors

- Individualize patient dosing needs

- Understand the mechanisms of drug interactions and prevent or anticipate their sequelae
Pharmacokinetics

- Describes the movement of drugs in the body
- Blend of math, physiology, pharmacology
- Four components:
  - Absorption, Distribution, Metabolism, Excretion (ADME)
Drug Absorption Occurs Via Many Routes of Administration

- Intravenous
- Subcutaneous
- Intramuscular
- Epidural
- Ocular
- Otic
- Rectal
- Dermal
- Oral/Enteral *
- Sublingual
- Buccal
- Intrasynovial
- Intranasal
- Vaginal

* This discussion pertains to enteral drug absorption
Enteral Drug Absorption

Generally a passive process, fueled by a concentration gradient transporting drugs from the gut into the portal circulation.

Significant types of pre-systemic clearance:
- Intestinal and hepatic metabolism
  i.e., via cytochrome P450 (CYP) enzymes
- Active transport via P-glycoprotein
- Resulting “first-pass effect”
GI drug absorption and pre-systemic metabolism

Fig. 2-2. A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement during gastrointestinal absorption. Incomplete dissolution or metabolism in the gut lumen or by enzymes in the gut wall is a cause of poor absorption. Removal of drug as it first passes through the liver further reduces absorption.
Oral/Enteral Drug Administration

Advantages:

- Avoids hazards of IV lines, infections, phlebitis
- Facilitates earlier ICU discharge (example - enteral methadone instead of fentanyl infusion)
- Lowers drug acquisition costs by an average of 8-fold

Caution! Drug bioavailability in critical illness may be deranged.
Oral/Enteral Drug Administration Should Be Avoided in Those With:

- Ileus, no active bowel sounds
- Ischemic bowel
- Gastric residuals
- Nausea and vomiting
- Malabsorption syndrome
- Questionable gut perfusion and poor hemodynamics
- Interacting substances in gut
Interacting GI Substances May Interfere with Absorption

Examples: **Phenytoin, quinolones, tetracyclines**

- Enteral nutrition with enteral phenytoin often lowers serum levels by as much as 80%.
  - Many patients require intravenous phenytoin to maintain adequate serum levels.
- Bi- and trivalent cations bind to quinolone and tetracycline antibiotics, potentially leading to treatment failures.
  - Avoid concurrent administration of substances such as iron, aluminum (sucralfate), magnesium, etc.
Distribution

Describes rate and extent of plasma transfer

Is determined by fat solubility and extent of protein binding

Relevance?

• Explains differences in onset of activity e.g., fentanyl vs. morphine
• Explains the prolonged duration of midazolam after long-term use
• Helps predict medication removal by renal replacement therapy
Drug entry and egress is a function of lipophilicity and the ability to cross the blood-brain barrier.

The onset and offset differences between morphine and fentanyl can be explained by the fact that fentanyl is 100 x more lipid soluble than morphine.
Why Does Midazolam Change From a Short- to a Long-acting Benzodiazepine When Given for a Prolonged Period of Time?

![Graph showing the duration of midazolam therapy and the corresponding extubation and CNS recovery times.]

Chest. 1993;103:55.
Accumulation in a deep compartment is a function of fat solubility and may explain the long duration of action of midazolam after long-term use.
How can the volume of distribution help predict removal by hemodialysis?

If a drug has a large volume of distribution, very little resides in the circulation and is available for removal via hemodialysis.

Examples - digoxin and tricyclic antidepressants

How about the extent of protein binding?

Highly protein bound drugs are typically not removed by hemodialysis.
The Clinical Relevance of Deranged Protein Binding of Drugs Has Been Overstated (Except for Phenytoin)

Pharmacologically active drug is in the “free” state, not protein bound

Normally, 90% phenytoin is protein bound and inactive (only 10% is “free”)

The free fraction of phenytoin increases with hypoalbuminemia and uremia

- Under these conditions, it is preferred to measure active drug i.e., “free” phenytoin levels, rather than “total” phenytoin levels.

P-glycoprotein (P-gp) and Drug Distribution

- Promiscuous ATP-dependent active transporter
  - evolved as a protective mechanism against a wide variety of toxic substances
- Located in intestine, renal tubule, biliary system, CNS, WBC, testes, tumor cell
- Relevance - acts as an efflux pump to limit absorption & distribution; expedites elimination of toxins (digoxin, etoposide, mitoxantrone, paclitaxel, tacrolimus)
  - Can P-gp inhibitors be used therapeutically for multidrug-resistant tumors?
  - May explain why quinidine and amiodarone double digoxin levels
The transmembrane protein **P-glycoprotein** is believed to function as an energy-dependent efflux pump or drug transporter.

**P-gp Inhibitors:**
- Verapamil
- Grapefruit juice
- Amiodarone
- Quinidine
- Clarithromycin
- Tariquidar

**P-gp Inducers:**
- Rifampin
- St. John’s Wort
Drug Metabolism

A.k.a. “biotransformation”

Refers to the “enzyme catalyzed changes in drug structure” or “the process by which drugs are converted \textit{in vivo} into one or more structural derivatives (metabolites)”

Sites - liver, gut, lungs, kidney, brain, plasma, skin

Originally viewed as detoxification reaction

↑ hydrophilicity which promotes excretion

May change the pharmacological activity or toxicity of the molecule
Consequences of Drug Metabolism

Substrate (drug) → Enzyme → Metabolite

Active → Inactive

Toxic → Nontoxic

Inactive → Active

Nontoxic → Toxic

Detoxification

Activation

Prodrug

Reactive metabolite
Phases of Drug Metabolism

Phase I

“Functionalization” reactions

Involve introduction or unmasking of a polar functional group (e.g., -OH, -NH$_2$, -SH, -COOH) on substrate to ↑ hydrophilicity and prepare for Phase II metabolism

Reaction classes:
- oxidation, reduction, hydrolysis

Oxidative metabolism mediated by cytochrome P450 (CYP) most important Phase I pathway!
“Conjugation” reactions

Involve addition of an endogenous compound (e.g., glucuronic acid, amino acid, acetyl group, sulfate) to functional group contained on drug molecule or product of Phase I metabolism

↑ hydrophilicity, detoxification, excretion

Reaction classes:
- glucuronidation, sulfation, glutathione conjugation, acetylation, methylation
Phases of Drug Metabolism

- Phase I: Phenol
- Phase II: Phenyl sulfate

Increasing polarity of drug/metabolite
Changes in drug metabolism are more commonly the result of *acquired* alteration of hepatocyte function via drug interactions than from *intrinsic* hepatic derangements.

May be genetically determined:
- Racial differences in functionality of many Phase I reactions (CYP 2D6, 2C9, 2C19, etc) *N Engl J Med. 2003;348:529.*
Cytochrome P450

- Most significant contributors to drug metabolism
- Catalyze biotransformation of endogenous substrates, dietary compounds, environmental chemicals, and up to 60% to 80% of drugs currently marketed!
- Present in species from bacteria to mammals; localized intracellularly in smooth endoplasmic reticulum
- > 270 gene families described; > 18 families in man
- CYP1, CYP2, and CYP3 families most clinically relevant
Contribution of CYP to Drug Metabolism

Drug Metabolism Often Results in Active Metabolites that Can Accumulate (Especially in Renal Disease)

- Normeperidine from meperidine
  • Epileptogenic
- Morphine 3- and 6-glucuronide salts
  • Prolonged narcosis
- Desacetylvecuronium from vecuronium
  • Prolonged paralysis
- Cyanide from nitroprusside
  • Death
- Hydroxymidazolam from midazolam
  • 66% the activity of the parent drug
Drug Excretion

Largely the domain of the kidney
  • Minor pathways: bile, lung, and feces

Common issue for drug dosing in the ICU
  • 7 - 25% ICU population develop significant renal impairment and many more have pre-existing renal disease
  • Age-related changes in organ function, including the kidneys
    • Approximately 1% functional loss per year after 30 years of age
Creatinine is freely filtered and serves as conventional surrogate for glomerular filtration.

The assumption is that there is a normal production of creatinine.

- **May not be true in catabolic, malnourished critically ill patients!**

MDRD equation derived from multiple regression analysis incorporates race, serum albumin, and urea nitrogen and may be more accurate *Ann Intern Med.* 1999;130:461.
Problem Drugs in Renal Disease

- Most cephalosporins and quinolones, imipenem, vancomycin, aminoglycosides, acyclovir, fluconazole
- Procainamide, digoxin, atenolol
- Meperidine, morphine, and midazolam
- Famotidine
- Milrinone
- Low molecular weight heparins
- Phenytoin (increased free fraction)
- Many drugs removed via renal replacement therapy (RRT)
  - Specifics vary with type of RRT and individual drugs
Pharmacokinetic Principles

- Steady-state: the amount of drug eliminated equals the amount of drug administered
- Results in a plateau or constant serum drug level
- Is a function of drug half-life
  - Steady-state occurs after 4 - 5 half-lives
Half-life

- Time it takes for half of an administered drug to be eliminated
- Defines the time needed for steady-state to occur and the time needed for complete elimination of drug from the body (4 - 5 half-lives)
Loading Doses

- Used to reach therapeutic levels quickly, especially if drug has long half-life
- Not affected by organ dysfunction
  - Except digoxin - use 75% typical loading dose
Simulated Serum Concentrations

Plasma Concentration vs. Time

Bolus + Infusion

Infusion
Linear Kinetics

- Constant fraction of total drug stores eliminated in a given time
- Almost all drugs follow linear kinetics (except in overdose situations)
- Dose increases result in proportional increases in serum levels
Non-linear Kinetics

- Constant **amount** (vs. %) eliminated per unit time
- Examples - phenytoin, aspirin, ethanol
- At point of metabolic limit, lose proportionality of dose with serum level
  - Example: 50% increase in phenytoin dose may result in 300% increase in level
Effect of increasing daily dose on steady-state drug concentrations for drugs undergoing nonlinear (---) and linear (.........) kinetics.
Contribution of Pharmagenetics to Interindividual Variability in Drug Response

Genetic polymorphisms in drug metabolizing enzymes, drug transporters, or receptors can cause clinically relevant effects on the efficacy and toxicity of drugs.
Clinical Relevance

- Most drugs are dosed on a “one-size-fits-all” basis
- Likely a major contributor to the high incidence of adverse drug reactions
- People can vary substantially in how they respond to a given drug!
Pharmacogenetics

The study of heredity as it relates to the absorption, distribution, elimination, and action of medicines

A tool to limit variability and individualize therapy
## Pharmacogenetics

<table>
<thead>
<tr>
<th>Drug-Metabolizing Enzyme</th>
<th>Frequency of Variant Poor-Metabolism Phenotype</th>
<th>Representative Drugs Metabolized</th>
<th>Effect of Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochrome P-450 2D6 (CYP2D6)</td>
<td>6.8% in Sweden, 1% in China</td>
<td>Debrisoquin[^15], Sparteine[^16], Nortriptyline[^23], Codeine[^27,28]</td>
<td>Enhanced drug effect, Enhanced drug effect, Enhanced drug effect, Decreased drug effect</td>
</tr>
<tr>
<td>Cytochrome P-450 2C9 (CYP2C9)</td>
<td>Approximately 3% in England (those homozygous for the *2 and *3 alleles)</td>
<td>Warfarin[^29,30], Phenytoin[^31,32]</td>
<td>Enhanced drug effect[^29-32]</td>
</tr>
<tr>
<td>Cytochrome P-450 2C19 (CYP2C19)</td>
<td>2.7% among white Americans, 3.3% in Sweden, 14.6% in China, 18% in Japan</td>
<td>Omeprazole[^34,35]</td>
<td>Enhanced drug effect[^36,37]</td>
</tr>
<tr>
<td>Dihydropyrimidine dehydrogenase</td>
<td>Approximately 1% of population is heterozygous</td>
<td>Fluorouracil[^38,40]</td>
<td>Enhanced drug effect[^38,40]</td>
</tr>
<tr>
<td>Butyrylcholinesterase (pseudocholinesterase)</td>
<td>Approximately 1 in 3500 Europeans</td>
<td>Succinylcholine[^41]</td>
<td>Enhanced drug effect[^9,41]</td>
</tr>
</tbody>
</table>

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

Clinical Consequences of Genetic Polymorphisms

Toxicity
- Can be profound for drugs with a narrow therapeutic index that are inactivated
  - mercaptopurine, fluorouracil

Reduced efficacy or therapeutic failure
- Drugs that are activated
  - codeine
Drug: Gene Interaction

Do allelic variants of drug metabolizing enzymes impact pharmacokinetics and response?

- Evaluated by Dalen et al, in 21 healthy Caucasian volunteers
- Nortriptyline is a tricyclic antidepressant metabolized by CYP2D6 to 10-hydroxynortriptyline.
Relationship between CYP2D6 genetic status and nortriptyline pharmacokinetics

Fig. 3. Mean plasma concentrations of a: nortriptyline and b: 10-hydroxynortriptyline in groups of subjects with different numbers of active CYP2D6 genes following a single oral dose of nortriptyline (NT). The number of CYP2D6 genes carried by individuals in each group are shown next to the curves. Modified figure, reproduced with permission from Ref. 31.

TIPS. 1999;20:342.
Utility of Pharmacogenetics

All patients with same diagnosis

1. Genetic profile for non-response or toxicity
   Treat with alternative drug or dose

2. Genetic profile for favorable response
   Treat with conventional drug or dose

Summary:
Management of Drug Therapy Using PK Principles

For each medication prescribed you need to know:

- Which organs are involved in drug clearance
- If genetic/race issues influence drug clearance
- Whether active metabolites are formed
- The half-lives of parent drug and metabolites to estimate time to steady-state (and therefore time for drug evaluation)
- Potential drug or food interactions
- If there is an oral or dermal formulation that patients can transition to if appropriate
Selected References

Case Scenario #1

- 23-year-old 100-kg male with multiple fractures and traumatic brain injury resulting from a motor vehicle crash
- 1800 mg (18 mg/kg) IV phenytoin load for seizure prophylaxis with maintenance dose of 300 mg IV every 12 hours (6 mg/kg/d); serum level = 10 mcg/ml day three of therapy
- Phenytoin suspension (same dose) begun when enteral nutrition initiated, with repeat phenytoin level in two days = 2 mcg/ml

Explain these findings

What strategy can we use to achieve therapeutic phenytoin levels?
The oral absorption of phenytoin may be dramatically reduced in the setting of enteral feeds.

Consider discontinuing phenytoin if treatment duration longer than seven days and if no seizures have occurred.

If continued prophylaxis indicated, offer phenytoin IV and avoid any GI absorption issues or advance the dose of enteral phenytoin (mindful that drug absorption will increase when a regular diet is resumed).
Case Scenario #2

68-year-old male post open heart surgery becomes acutely agitated and is treated successfully with 3 mg midazolam IV.

Requires additional CV support in the form of an IABP and experiences more consistent agitation treated with a continuous infusion of midazolam 8mg/hr for three days.

CV status improves and he is ready to extubate. Midazolam is discontinued, but he remains in a drug-induced stupor for three days.

Why?
Midazolam’s lipophilicity and ability to enter the CNS explain its rapid onset and offset with acute use.

Lipophilicity (and accumulation in adipose tissue) can also explain midazolam’s prolonged duration of action with long-term use.

An additional confounder is the formation and potential accumulation of the active hydroxy-midazolam metabolite.

Because of this, SCCM suggests that lorazepam is the preferred benzodiazepine for long-term use.
Case Scenario #3

- 60-year-old male recovering from acute coronary syndrome receives aggressive LDL therapy - simvastatin, 80 mg daily
- His med list includes NTG, ASA, an ACE inhibitor, amiodarone
- Within three days he experiences extreme muscle pain with a CK of 20,000.
- What is the pharmacologic explanation for these findings?
Most statins are metabolized by CYP 3A4 and are susceptible to drug interactions.

Amiodarone (and many other drugs) interfere with CYP 3A4 function and may lead to statin toxicity - perhaps even to rhabdomyolysis.

Simvastatin dosing should be limited to 20 mg daily or less in these circumstances.