Pharmacokinetics and Toxicokinetics

Howard A. Greller, MD FACEP FACMT

North Shore University
Department of Emergency Medicine
Division of Medical Toxicology
WHAT WE’LL COVER TODAY

• Pharmacokinetics/Toxicokinetics
  • Absorption
  • Distribution
  • Metabolism
  • Elimination
• Pharmacodynamics/Toxicodynamics
  • Xenobiotic interactions
• Pharmacogenomics/Toxicogenomics
ABSORPTION

• Process by which a xenobiotic enters body

• Rate of absorption (ka) determined by:
  • Route of administration
  • Dosing form
  • Bioavailability
ROUTE OF ABSORPTION

- Affects rate and extent
- IV, inhalation > IM, SQ, IN, PO > SQ, PR
- Onset dependent on route
ROUTE OF ABSORPTION

Oral, onset approximately 20 minutes
ROUTE OF ABSORPTION

Smoking ~10 seconds, IV ~30 seconds
DISSOLUTION
DIFFUSION
DISINTEGRATION
EROSION
OSMOTIC PUMPS
ION EXCHANGE RESINS
BIOAVAILABILITY

- Amount reaches systemic circulation, unchanged
- Extent of absorption
  - Predicts intensity of effect
- First pass effects modify bioavailability
FIRST PASS EFFECTS

- Prevention of absorption
- Decon / chelation (+/-)
- P-glycoprotein
- Bezoars, mod preps
- Pre-systemic metabolism
  - Hepatic, gastric mucosa, intestinal BB
  - Bacterial
- Saturable in overdose
FIRST PASS EXAMPLES

- Gastric emptying time
  - Food, medications
- Gastric ADH
  - Age, sex, H2
  - “worst case”
- High FP ("low bioavailability")
  - Propranolol, cyclosporine, morphine, TCAs
IONIZATION

- **Uncharged, non-polar** cross membranes
  - pH + pKa (dissociation constant) determine ionization (HH)
  - \( \log (HA/A^-) = pK_a - pH \)
  - \( HA/A^- = 10^{pK_a-pH} \)
  - pH < pK_a \( \Rightarrow \) HA/A^- > 1
    - Favors *non-ionized*
  - pH > pK_a \( \Rightarrow \) HA/A^- < 1
    - Favors ionized
• Weak acid (pKa 3.5)

**What is HA/A- in urine for pH=3.5? 7.5?**
ION TRAPPING

- $HA/A^- = 10^{pK_a-pH}$
- $pH 3.5 = (10^{3.5-3.5}) = 10^0 = 1 = 1:1$
- $pH 7.5 = (10^{3.5-7.5}) = 10^{-4} = 1/10,000$
  - With alkalinization, ionized, “trapped”
LIPID SOLUBILITY

- Partition coefficients (oil/water)
- Higher lipid solubility, higher absorption
- Even with similar pK\textsubscript{a}
- Thiopental >> secobarbital >> barbital
- All with pK\textsubscript{a} of ~7.8
SURFACE AREA

- Affected by blood flow
  - Hypotension
  - Vasoconstriction
SPECIALIZED TRANSPORT

• Active (energy dependent)
  • Transport against a concentration gradient
• Facilitated (energy independent)
• Xenobiotics utilize native systems
  • 5-FU resembles pyrimidine
  • Thallium/Pb resemble $K^+$ and $Ca^{2+}$
P-GLYCOPROTEIN (PGP)

- Active **efflux** transporter (inside out) - “ABC” family
  - BBB, BTB, brush border

**S**
- Digoxin, protease inhibitors, vinca alkaloids, paclitaxel

**STOP**
- Amiodarone, ketoconazole, quinidine, verapamil

**+**
- St. John’s wort
Well, Mr. Brown... I hope your attitude's as positive as these test results.
VOLUME OF DISTRIBUTION

• Where the drug goes
  
  • $V_d \ (L/kg) = \frac{\text{amount}}{C_p} = \frac{S \times F \times \text{dose}}{C_0}$

$[C] = \frac{(S \times F \times \text{dose})}{(V_d \times \text{kg})}$

• Apparent proportionality constant
  
  • Not a real volume (i.e. chloroquine $\sim 185 \ L/kg$)
SOME EXAMPLES

Large Vd (>1 L/kg)
- Antidepressants
- Camphor
- Digoxin
- Opioids
- Phencyclidine
- Phenothiazines

Small Vd (<1 L/kg)
- Alcohols
- Lithium
- Phenobarbital
- Phenytoin
- Salicylate
- Valproic acid
ONE COMPARTMENT MODEL

Change in [plasma] = change [tissue]
TWO COMPARTMENT MODEL

- Measure #1
- Effects in #2
- Examples
  - Digoxin
  - Lithium
- There can be multiple, multiple compartments ...
MODIFIERS

• Lavage, AC and WBI $\downarrow$ Ka
• MDAC, ion-trapping, chelation $\uparrow$ Ke
  • Decrease $C_{\text{max}}$, $t_{\text{max}}$ and AUC
• Extracorporeal techniques $\uparrow$ Ke
DISTRIBUTION ≠ SITE OF TOXICITY / ACTION

- Lead ➔ bone
- DDT ➔ fat

vs

- CO ➔ Hgb
- Paraquat ➔ type II alveolar
PROTEIN BINDING

- Phenytoin 90% bound with normal albumin
  - Albumin decreases, more free active drug

- \([\text{phenytoin}] = 14 \text{ mg/L} (10-20 \text{ mg/L})\)

- **Sick** (2 g/dL) vs. **Healthy** (4 g/dL)

- \([\text{adjusted}] = \frac{[\text{measured}]}{(0.25 \times \text{albumin}) + 0.1}\)

- **23.33 mg/L** vs. **12.73 mg/L**
PROTEIN BINDING - ASA

• Overdose increases apparent $V_d$
  • ↑ free drug → lower pH ↑ HA ↑ diffusion
  • More drug in tissues, more toxicity
• Other drugs with high protein binding
  • Carbamazepine, valproate, warfarin, verapamil
POOR LITTLE JOHNNY . . .

• Johnny got dumped
  • He went home and took grandma’s digoxin
• Grandma calls poison control
• Do we have to be worried?
  • Johnny weighs 50 kg
  • Grandma’s pills are 250 mcg each
  • There were 25 of them left . . .
WORST CASE SCENARIO . . .

- $[C] = \frac{(S \times F \times \text{dose})}{(Vd \times \text{kg})}$
  
  $= \frac{(1 \times 0.7 \times 25 \times 0.25\text{mg})}{(6\text{L/kg} \times 50\text{kg})}$
  
  $= \frac{4.38\text{mg}}{300\text{L}} = 0.015\text{mg/L}$

- *Units, units, units . . .*
  
  $= (0.015\text{mg/L}) \times (106\text{ng/mg}) \times (1\text{L/1000mL})$

- $[\text{digoxin}] = 15\text{ ng/mL (worry)}$
HOW MUCH FAB?

- TBL (total body load) = $S \times F \times \text{dose}$
- $1 \times 0.7 \times (25 \times 0.25 \text{ mg}) = 4.375 \text{ mg}$
- Each vial binds 0.5 mg digoxin
- Therefore, need 9 vials based on dose
- Worst case $([C] \times \text{kg})/100 = 8 \text{ vials}$ (round up)
HIS LEVEL IS 4 NG/ML . . .

• Dose = Vd \times C_p; \text{ Vd} = 6 \text{ L/kg}; \text{ wt} = 50 \text{ kg};
0.5\text{mg digoxin bound / vial}

\[
\text{Dose} = (6 \text{ L/kg}) \times (50 \text{ kg}) \times (4 \text{ ng/mL}) = 1200 \ldots 1200 \text{ what?}
\]

\[
(10^3 \text{ mL/l L}) \times (6 \text{ L/kg}) \times (50 \text{ kg}) \times (4 \text{ ng/mL}) \times (1 \text{ mg/10}^6 \text{ ng})
\]

= 1.2 \text{ mg}

• 0.5 \text{ mg/vial} = 3 \text{ vials (round up)}

• Shorthand \([C] \times \text{kg})/100 = 2 \text{ vials}
CHARLIE ONE-ON-ONE
SHEEN: “I’M FINE. I’VE ALWAYS HAD A PLAN.”
METABOLISM
METABOLISM

• “Morally” neutral
  • Toxicate vs detoxify vs biotransform

• **LEO GER** (CYP 450)
  • Oxidize substrate (**lose e**
  • Reduce electrophile (**gain e**

• Cyclical oxidation co-factor
  • i.e. NADH / NAD$^+$
  • Links catabolism to synthesis
PHASE I (PREPARATORY)

- Add/expose polar groups
- Hydrolysis
  - Esterase, peptidase, epoxidase
- Oxidation
  - P450, ADH, MAO, etc.
- Reduction
  - Azo-, Nitro-, Carbonyl-, Quinone
- Dealkylation
**PHASE I EXAMPLES**

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{NADPH} + \text{H}^+ + \text{O}_2 \xrightarrow{\text{CYP2E1}} \text{CH}_3\text{CHO} + \text{NADP}^+ + 2\text{H}_2\text{O}
\]

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{NAD}^+ \xrightarrow{\text{Alcohol Dehydrogenase}} \text{CH}_3\text{CHO} + \text{NADH} + \text{H}^+
\]

(F) Transesterification (cocaine)

*Casarett & Doull’s 7th Edition*
PHASE II (SYNTHETIC)

• Conjugation polar groups
  • ↑ hydrophilicity
• Glucuronide, acetate, sulfate, methyl, amino acids and glutathione
• GAS MAG
CYP 450 INTERACTIONS

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007)
http://medicine.iupui.edu/clinpharm/ddis/table.aspx
Accessed 3/2012
### CYP 1A2

- **Aryl Hydrocarbon Hydroxylase**
- 15% pharmaceuticals
- Linked with cancer

#### Substrates
- Caffeine
- Carvedilol
- Clozapine
- Theophylline
- R-warfarin
- APAP
- Haloperidol

#### Inducers
- broccoli & brussel sprouts, *cigarettes*, char-grilled meat, insulin, modafinil, omeprazole

#### Inhibitors
- fluvoxamine, ciprofloxacin
- amiodarone, cimetidine, clarithromycin, interferon, ticlodipine

#### Toxication
- APAP, benzo[a]pyrene, dichloromethane
### CYP 2C9

**Inducers**
- rifampin, secobarbital

**Inhibitors**
- fluconazole, amiodarone, fluvoxamine, isoniazid, lovastatin, sertraline, sulfamethoxazole

**Toxication**
- Phenytoin & warfarin (decreased metabolism)

**Most abundant CYP2C Substrates**
- NSAID’s
- S-warfarin
- Sulfonylureas
- Phenytoin
- ARBs
**CYP 2C19**

Absent 20% Asians
“PPIs & Seizures”

<table>
<thead>
<tr>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine, prednisone, rifampicin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>omeprazole, cimetidine, fluoxetine, indomethacin, ketoconazole, modafinil, oxcarbazepine, ticlodipine, topiramate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Substrates**

- Diazepam
- Phenytoin
- Phenobarbital
- **Omeprazole**
- R-warfarin
- Carvedilol
## CYP 2D6

25% drugs, 50% antipsych
10% W, 8% AA poor metab
Ethiopian ultra-rapid metab

### Inducers
- Dexamethasone, rifampin

### Inhibitors
- Bupropion, fluoxetine, paroxetine, quinidine, sertraline, duloxetine, amiodarone, cimetidine, citalopram, cocaine, doxorubicin, h₁ antagonists, methadone, metoclopramide, ritonavir

### Substrates
- β-blockers
- Codeine
- Methadone, oxycodone, codeine
- Tamoxifen
- TCAs, SSRIs
- Haloperidol

### Toxica9on
### CYP 2E1

**7% total CYP in liver**

Only other CYP cancer (1A2)

- NP CA in Chinese smokers

**Substrates**

- **Acetaminophen**
- Anesthetics
- Ethanol
- Theophylline

**Inducers**

- ethanol (chronic), fomepizole, isoniazid, phenobarbital, phenytoin, cigarette smoke

**Inhibitors**

- disulfiram, diethyl-dithiocarbamate, ethanol (acute), fomepizole

**Toxication**

- acetaminophen, ifosfamide, acrylonitrile, CCl₄, aniline, benzene, dichloromethane, vinyl chloride
CYP 3A4

- Most abundant CYP in liver
- Most common intestinal
- 50-60% all pharmaceuticals
- Terfenadine + erythromycin

**Inducers**
- carbamazepine, efavirenz, modafinil, glucocorticoids, oxcarbazepine, phenobarbital, phenytoin, rifampin, st. john’s wort

**Inhibitors**
- protease inhibitors, clarithromycin, ketoconazole, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, ciprofloxacin, fluvoxamine, starfruit

**Toxication**
- acetaminophen, aflatoxin
# P-Glycoprotein

## Inducers
- rifampin, st. john’s wort

## Inhibitors
- amiodarone, cyclosporine, ketoconazole, quinidine, ritonavir, tamoxifen, verapamil

## Substrates
- Cyclosporine
- Digoxin
- Diltiazem
- Loperamide
- Lovastatin

## Toxication
best Venn diagram ever

Times When I'm Truly Happy

Times When I'm Wearing Pants
ELIMINATION
ELIMINATION

• Biotransformation, clearance, excretion

• Clearance(ss) = elimination ~ concentration
  • $Cl = \frac{k_e}{C}$

• Clearance is additive
  • Hepatic + renal + GI + etc.
ELIMINATION

• Clearance constant over concentration
  • i.e. elimination not saturated
• Rate is proportional to concentration
  • $k_e = Cl \times C$
• First order elimination
  • Calculate clearance from AUC (dose/AUC)
FIRST ORDER

- **Percentage** eliminated / time is constant
  - Linear on semi-log paper
- $t_{1/2}$ is time for 50% reduction
  - $t_{1/2} = 0.693/k_e = 0.693 \times V_d/Cl$
MICHAELIS-MENTEN

• “In between” elimination
  • Elimination related to concentration
  • $k_e = (V_{\text{max}} \times C)/(k_m + C)$
    • $V_{\text{max}}$ – maximum elimination capacity
    • $k_m$ – concentration at 50% of $V_{\text{max}}$
  • Non-linear
FIRST ORDER

- When concentration is low ($C \ll k_m$)
  \[ k_e = \frac{(V_{\text{max}} \times C)}{(k_m + C)} = \frac{V_{\text{max}}}{k_m} \]
- Process is **not** saturated
  - First order
ZERO ORDER

• When concentration is high \((C >> \text{km})\)
  \[ k_e = \frac{(V_{\text{max}} \times C)}{(k_m + C)} = V_{\text{max}} \]

• Fixed amount eliminated per time
  • Elimination \textit{saturated}, capacity limited

• Non-linear; no “half-life”

• Dose >> elimination, no steady state
  • Concentration keeps rising with dose
GRAPHS YOU SHOULD KNOW

- First Order
- Zero Order
- Michaelis Menten
“ENHANCED” ELIMINATION

- Johnny takes dad’s Enditall™
  - His serum concentration is 1000 ng/mL
  - $V_d = 40 \text{ L/kg}$
- PCC recommends hemodialysis
  - Dialysis flow rate = 300 mL/min
  - $C_{out} (HD) = 340 \text{ ng/mL}$
- Johnny weighs 100 kg
“HALF LIFE” ON HD?

- Clearance = flow x ER (extraction ratio)
  - ER = (C\text{in} - C\text{out})/C\text{in} = (1000-340)/1000
  - flow x ER = 300 x 2/3 = 200 mL/min
- So what’s the half-life on HD?
  - \( t_{1/2} = 0.693 \times V_d/Cl = (0.693 \times 40\text{L/kg} \times 100 \text{ kg})/(200 \text{ mL/min} \times 60 \text{ min/hr} \times 0.001 \text{ L/mL}) \)
  - 231 hours!
WHAT DID WE MISS?

• Clearance is sum of **ALL** clearances

• \( \text{Cl}_{\text{total}} = \text{Cl}_{\text{native}} + \text{Cl}_{\text{HD}} \)
  
  • = (90 L/hr) + (12 L/hr) = 102

• \( t_{1/2} = (0.693 \times 4000 \text{ L})/(102 \text{ L/hr}) = \)
  
  • 27.2 hours (better)
WHAT ABOUT CRRTS?

- $Cl = \frac{\text{Volume/time of UF}}{\text{UF}} \times \frac{C_{UF}}{C_p}$

- Usual renal clearance for lithium is 25-35 mL/min

- HD adds about 100-150 mL/min
  - Only 4 hours at a time, plus rebound

- CVVH adds 20-35 mL/min, continuously
  - Clear ~ 50 L/day vs. 36 L/day with 4 hr HD
  - Plus, no rebound
FOR HELP
1. Push RED BUTTON
2. Or YELL
PHARMACODYNAMICS AND TOXICODYNAMICS
TIME COURSE DRUG ACTION

• Drug (D) - receptor (R) interaction

• \([D] + [R] \leftrightarrow [DR]\)

  • \(K_{\text{dissociation}} = \frac{[D][R]}{[DR]}\)

• Effect (E) proportional to occupancy . . .

  • \(E = \frac{[D]}{(K_d + [D])}\)
DOSE RESPONSE CURVE

- log-log plot of $E = \frac{[D]}{(K_d+[D])}$
  - Sigmoid shaped, linear in middle
- When $E = 50\%$, dose $= K_d$
KINETICS VS. DYNAMICS

• Dynamics = time course of effect at receptor
• Kinetics = concentration in central compartment
• When xenobiotic is bound to receptor, it no longer participates in kinetic process
PENTOBARBITAL

- Terminal half-life is long (6-48 hours)
- Yet, patients wake up minutes after bolus
- Highly lipid soluble
  - Rapidly $\rightarrow$ highly perfused tissues (brain)
  - Redistributes to low-perfusion, high volume tissue (fat)
  - Central concentration is not reflective of receptor concentration (clinical effect)
ORGANOPHOSPHATE

• Half-life of parathion is short
• Cholinesterase inhibited days to weeks
  • Binding functionally irreversible
  • Kinetics at receptor not reflected by serum concentration
• Irreversible binding or sequestration separates kinetic from dynamic process
APAP

• Dynamic time ≠ equal kinetic time
• APAP half-life is ~ 4 hours
  • Toxicity manifests days later
• Kinetics depends on metabolism
• Dynamics is a function of the time course of interactions
  • Cellular injury, immune response, etc
OTHER EXAMPLES OF PK ≠ PD

• OPIDN (“Jake Leg”, disrupted neuronal transport)
• Delayed axonal injury in CO (demyelination)
• Carcinogenesis (multifactorial)
• Physostigmine (hysteresis)
FENGA PAPIT
RECEPTORS

• Agonism – mimics natural ligand
• Antagonism – opposes natural ligand
• Agonist/antagonist (partial effect)
  • Less effective ligand than natural ligand
  • Natural ligand missing, mostly activation
  • Natural ligand present, mostly antagonism
RECEPTOR LIGAND INTERACTIONS

• Competition - naloxone
  • Fight for the same receptor site
  • More of either overwhelms the other

• Non-competitive - flumazenil
  • Binding to different sites changes the effect
  • Adding more does not result in more effect
RECEPTOR LIGAND INTERACTIONS

• Un-competitive inhibition - lithium
  • Inhibitor binds enzyme-substrate complex
  • The more substrate, the more inhibited
RECEPTOR REGULATION

• Cell surface and nuclear receptors
  • Self-regulate in response to signals
  • Over-stimulated down-regulate, etc
• Important in tolerance and withdrawal
  • Chronic cocaine ↑ dopamine receptors
  • GABA ↓, NMDA ↑ with chronic ethanol
I used to think correlation implied causation.

Then I took a statistics class. Now I don't.

Sounds like the class helped. Well, maybe.
TOLERANCE AND WITHDRAWAL
BIOLOGIC TOLERANCE

- Diminished effect with repeat administration
- Withdrawal
  - Physiologic symptoms after discontinuation
- Physiologic tolerance
  - Receptor regulation / metabolic changes
- Behavioral (independent of physiology)
TOLERANCE VS. ADDICTION

- Tolerance = physiologic adaptation
- Addiction = behavior directed at avoiding withdrawal
  - Usually in tolerant individuals
  - Continued use, seeking behavior despite adverse consequences
Sometimes I feel that I have the worst job in the world!

Ya...right.
ADVERSE EFFECTS
XENOBIOTIC INTERACTIONS
ADVERSE DRUG EVENTS

• 1.5 million ADE/yr in U.S. (>1/d/pt)
• Predictable
  • Pharmacokinetic/dynamic
• Immunologic
  • I-IV, hepatitis
UNPREDICTABLE
(IDIOSYNCRATIC)

- Polymorphisms ("fast metabolizers")
  - epoxide hydrolase + phenytoin = anticonvulsant hypersensitivity
  - N-acetyl-transferase + INH = neuropathy, hepatitis
  - G6PD + pyridium = hemolysis
XENOBIOTIC INTERACTIONS

- Food
  - Fluoroquinolone (FQ) + antacid = decreased absorption of FQ
  - Tyramine and MAOI = hypertensive crisis
  - Warfarin and cruciferous veggies = ↑ INR
- Flora
  - ABX + e. lentum + digoxin = increased digoxin (less digestion)
- Distribution
  - Amiodarone + phenytoin = protein binding
XENOBIOTIC INTERACTIONS

• Metabolism
  • Rifampin + carbamazepine (CBZ) = decreased CBZ (3A4)
  • Grapefruit + 3A4 substrate = ↑ levels

• Excretion
  • NSAIDs + lithium = ↑ lithium

• Pharmacodynamics
  • PGE-5 inhibitor (sildenafil) + nitrates = hypotension
  • SSRI & MAOI = serotonin syndrome
  • Terfenadine and erythromycin = prolonged QT
GENOMICS
PROTEOMICS
LIFE EXPLAINED . . .

• Step 1
  • Genomics
  • “Possibilities”

• Step 2
  • Transcriptomics
  • Selected outcomes

• Step 3
  • Proteomics
  • Equipment

• Step 4
  • Metabolomics
  • Results (biochem)
PROFILING (THE FUTURE . . .)

• Applied genomics, proteomics, etc.
  • Identify mechanisms of toxicity
  • Reduced animal testing
• Genotype patients
  • Early diagnosis of disease or predisposition
  • Predict ADRs, idiosyncratic reactions
• Custom therapeutics, correct dosing
  • CYP2D6 and codeine