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

OVERVIEW

Dose
Absorption
Liberation
Drug
Protein
Biotransformation
Tissue
Elimination
Excretion
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
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-) = pKa - pH
  - $HA/A^- = 10^{pK_a-pH}$
  - pH < pKa $\Rightarrow$ HA/A- > 1
    - Favors non-ionized
  - pH > pKa $\Rightarrow$ HA/A- < 1
    - Favors ionized

SALICYLATE

- Weak acid (pKa 3.5)

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

- $\frac{HA}{A^-} = 10^{pKa-pH}$
- $pH 3.5 = (10^{3.5-3.5}) = 10^0 = 1 = 1:1$
- $pH 7.5 = (10^{3.5-7.5}) = 10^{-4} = 1/10,000$
  - With alkanization, ionized, “trapped”

LIPID SOLUBILITY

- Partition coefficients (oil/water)
- Higher lipid solubility, higher absorption
- Even with similar $pK_a$
  - Thiopental $>>$ secobarbital $>>$ barbital
- All with $pK_a$ 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 Ca²⁺

P-GLYCOPROTEIN (PGP)

- Active efflux transporter (inside out) - “ABC” family
  - BBB, BTB, brush border
  - Digoxin, protease inhibitors, vinca alkaloids, paclitaxel
  - Amiodarone, ketoconazole, quinidine, verapamil
  - St. John’s wort

Well, Mr. Brown... I hope your attitude's as positive as these test results.

Cyanide and Happiness © Explosm.net
DISTRIBUTION

VOLUME OF DISTRIBUTION

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

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

- Apparent proportionality constant
  - Not a real volume (i.e. chloroquine ~185 L/kg)

SOME EXAMPLES

<table>
<thead>
<tr>
<th>Large $V_d \ (&gt; 1 \ L/kg)$</th>
<th>Small $V_d \ (&lt; 1 \ L/kg)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Alcohols</td>
</tr>
<tr>
<td>Camphor</td>
<td>Lithium</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Opioids</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Salicylate</td>
</tr>
<tr>
<td>Phentiazines</td>
<td>Valproic acid</td>
</tr>
</tbody>
</table>
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 ↓ Ka
- MDAC, ion-trapping, chelation ↑ Ke
- Decrease $C_{max}$, $t_{max}$ and AUC
- Extracorporeal techniques ↑ Ke
**DISTRIBUTION ≠ SITE OF TOXICITY / ACTION**

- Lead ➔ bone
- DDT ➔ fat
- CO ➔ Hgb
- Paraquat ➔ type II alveolar

**PROTEIN BINDING**

- Phenytoin 90% bound with normal albumin
- Albumin decreases, more free active drug
- [phenytoin] = 14 mg/L (10-20 mg/L)
  - **Sick** (2 g/dL) vs. **Healthy** (4 g/dL)
  - [adjusted] = [measured] / ((0.25 x 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 . . .
  \[ = (0.015\text{mg/L}) \times (106\text{ng/mg}) \times (1\text{L}/1000\text{mL}) \]
- \([\text{digoxin}] = 15 \text{ ng/mL (worry)}\)
HOW MUCH FAB?

- TBL (total body load) = S x F x dose
- 1 x 0.7 x (25 x 0.25 mg) = 4.375 mg
- Each vial binds 0.5 mg digoxin
- Therefore, need 9 vials based on dose
- Worst case ([C] x kg)/100 = 8 vials (round up)

HIS LEVEL IS 4 NG/ML . . .

- Dose = Vd x Cp; Vd = 6 L/kg; wt = 50 kg; 0.5mg digoxin bound / vial
- Dose = (6 L/kg) x (50 kg) x (4 ng/mL) = 1200 . . . 1200 what?
  (10^3 mL/1 L) x (6 L/kg) x (50 kg) x (4 ng/mL)
  x (1 mg/10^6 ng)
  = 1.2 mg
- 0.5 mg/vial = 3 vials (round up)
- Shorthand ([C] x kg)/100 = 2 vials
METABOLISM

- "Morally" neutral
  - Toxicate vs detoxify vs biotransform
- **L**EO **G**ER (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
  - **H**ydrolysis
    - Esterase, peptidase, epoxidase
  - **O**xidation
    - P450, ADH, MAO, etc.
  - **R**eduction
    - Azo-, Nitro-, Carbonyl-, Quinone
  - De-alkylation
**PHASE I EXAMPLES**

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{OH} + \text{NADPH} + \text{H}^+ + \text{O}_2 & \rightarrow \text{CH}_3\text{CHO} + \text{NADP}^+ + 2\text{H}_2\text{O} \\
\text{CH}_3\text{CH}_2\text{OH} + \text{NAD}^+ & \rightarrow \text{CH}_3\text{CHO} + \text{NADH} + \text{H}^+
\end{align*}
\]

**CYP2E1**

**Alcohol Dehydrogenase**

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**PHASE II (SYNTHETIC)**

- Conjugation polar groups
- ↑ hydrophilicity
- Glucuronide, acetate, sulfate, methyl, amino acids and glutathione
- GAS MAG

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**CYP 450 INTERACTIONS**


Pharmacokinetics and Toxicokinetics
### 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,
  - ticlopidine

**Toxication**
- APAP, benzo[a]pyrene,
  - dichloromethane

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### CYP 2C9

**Most abundant CYP2C**

**Substrates**
- **NSAID’s**
- **S-warfarin**
- Sulfonylureas
- Phenotoin
- ARBs

**Inducers**
- rifampin, secobarbital

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

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

### CYP 2C19

**Absent 20% Asians**
- **“PPIs & Seizures”**

**Substrates**
- Diazepam
- Phenotoin
- Phenobarbital
- **Omeprazole**
- R-warfarin
- Carvedilol

**Inducers**
- carbamazepine, prednisone,
  - rifampicin

**Inhibitors**
- **omeprazole**, cimetidine,
  - fluoxetine, indomethacin,
  - ketoconazole, modafinil,
  - oxcarbazepine, ticlopidine,
  - topiramate

**Toxication**

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### CYP 2D6

#### 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

#### Toxication

### CYP 2E1

#### Inducers
- Ethanol (chronic), fomepizole, isoniazid, phenobarbital, phencytoin, cigarette smoke

#### Inhibitors
- Disulfiram, diethyl-dithiocarbamate, ethanol (acute), fomepizole

#### Substrates
- Acetaminophen
- Anesthetics
- Ethanol
- Theophylline

#### Toxication

### CYP 3A4

#### 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

#### Substrates
- Benzos
- Dapson
- Ca²⁺ block
- Ziprasidone
- Haloperidol
- HIV viral
- HMG CoA
- Immune
- Macro (≠ Az)
- Methadone
- Modafinil

#### Toxication
- Acetaminophen, aflatoxin
P-GLYCOPROTEIN

Inducers
rifampin, st. john’s wort

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

Toxication

Substrates
• Cyclosporine
• Digoxin
• Diltiazem
• Loperamide
• Lovastatin

ELIMINATION

Pharmacokinetics and Toxicokinetics

• best Venn diagram ever

Times When I’m Truly Happy

Times When I’m Wearing Pants

Times When I’m Truly Happy
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
  - \( t_{1/2} = \frac{0.693}{k_e} = 0.693 \times V_d/Cl \)
FIRST ORDER

MICHAELIS-MENTEN

- "In between" elimination
- Elimination related to concentration
- $k_e = \frac{V_{max} \times C}{(k_m + C)}$
  - $V_{max}$ – maximum elimination capacity
  - $k_m$ – concentration at 50% of $V_{max}$
  - Non-linear

FIRST ORDER

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

- When concentration is high ($C \ll \ll \ll k_m$)
  
  $$k_e = \frac{V_{\text{max}} \times C}{k_m + C} \approx V_{\text{max}}$$

- Fixed amount eliminated per time
  
  - Elimination saturated, capacity limited
  
  - Non-linear; no “half-life”

- Dose $\gg$ 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
  
  - $C_{\text{out}} \text{ (HD)} = 340 \text{ ng/mL}$

  - 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\text{1/2} = 0.693 x V\text{d}/Cl = (0.693 x 40L/kg x 100 kg)/(200 mL/min x 60 min/hr x 0.001 L/mL)
  - 231 hours!

**WHAT DID WE MISS?**

- Clearance is sum of ALL clearances
  - Cl\text{total}= Cl\text{native} + Cl\text{HD}
    - = (90 L/hr) + (12 L/hr) = 102
  - t\text{1/2} = (0.693 x 4000 L)/(102 L/hr) =
    - 27.2 hours (better)

**WHAT ABOUT CRRTS?**

- Cl = (Volume/time of UF) x (C\text{UF}/C\text{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
TIME COURSE DRUG ACTION

- Drug (D) - receptor (R) interaction
- \([D] + [R] \rightleftharpoons [DR]\)
- \(K_{\text{dissociation}} = [D][R]/[DR]\)
- Effect (E) proportional to occupancy . . .
- \(E = [D]/(K_d + [D])\)
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)
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 overpowers 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
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
ADVERSE EFFECTS
XENOBIOTIC INTERACTIONS

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 + pyrimidium = 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
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

Questions?