Pharmacokinetics and Toxicokinetics

Howard A. Greller, MD FACEP FACMT

DISCLOSURE

WHAT WE’LL COVER TODAY

- Pharmacokinetics/Toxicokinetics
- Absorption
- Distribution
- Metabolism
- Elimination
- Pharmacodynamics/Toxicodynamics
- Xenobiotic interactions
- Pharmacogenomics/Toxicogenomics
OVERVIEW

- 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 > SL > IM, SQ, IN, PO > CU, PR
- Onset dependent on route
ROUTE OF ABSORPTION

Oral, onset approximately 20 minutes

---

ROUTE OF ABSORPTION

Smoking ~10 seconds, IV ~30 seconds

---

DISSOLUTION
OSMOTIC PUMPS

ION EXCHANGE RESINS

BIOAVAILABILITY

• Amount reaches systemic circulation, unchanged
• Extent of absorption
  • Predicts intensity of effect
  • First pass effects modify bioavailability
BEZOARS & CONCRETIONS

- Anticholinergics
- Barbiturates
- Bromides
- Enteric-coated tablets
- Glutethimide
- Iron
- Meprobamate
- Methaqualone
- Opioids
- Phenytoin
- Salicylates
- Verapamil

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/ = H A-
- pH < pK a, H A/ > 1
  - Favors non-ionized
- pH > pK a, H A/ < 1
  - Favors ionized

Weak acids donate protons
Weak bases accept protons
When pH=pKa, half is protonated, half is unprotonated
A weak acid is protonated (has a proton, is uncharged) at a pH that is less than the pKa (i.e. an acidic environment), and thus is more likely to cross biologic membranes
An acid with a low pKa is a strong acid (that is it gives up its protons very easily unless the surrounding pH is very low - the pH is more likely to favor donation of the proton)
A weak base is protonated (has a proton, is uncharged) at a pH that is greater than the pKa (i.e. a basic environment), and thus is more likely to cross biologic membranes
A base with a high pKa is a strong base (that is it accepts a proton very easily from the environment unless the pH is very high - the pH is more likely favor accepting a proton)

SALICYLATE

- Weak acid (pKₐ 3.5)

<table>
<thead>
<tr>
<th>pH</th>
<th>Brain</th>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.8</td>
<td>SH</td>
<td>SH</td>
<td>SH</td>
</tr>
<tr>
<td>7.4</td>
<td>H⁺ + S⁻</td>
<td>H⁺ + S⁻</td>
<td>H⁺ + S⁻</td>
</tr>
</tbody>
</table>

What is HA⁻ 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 \quad 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
  - $V_d \ (L/kg) = \frac{\text{amount}}{C_p} = \frac{S \times F \times \text{dose}}{C_0}$

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

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

SOME EXAMPLES

- Large $V_d \ (>1 \ L/kg)$
  - Antidepressants
  - Camphor
  - Digoxin
  - Ethanol
  - Phenacyclidine
  - Phenothiazines

- Small $V_d \ (<1 \ L/kg)$
  - Alcohol
  - Lithium
  - Phenobarbital
  - Phenytoin
  - Salicylate
  - Valproic acid
ONE COMPARTMENT MODEL

\[ \text{Change in [plasma]} = \text{change [tissue]} \]

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 \( C_{\text{max}}, t_{\text{max}} \) and AUC
- Extracorporeal techniques ↑Ke
DISTRIBUTION ≠ SITE OF TOXICITY / ACTION

- Lead ➔ bone vs CO ➔ Hgb
- DDT ➔ fat vs 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; 0.5 mg digoxin bound / vial
  Dose = (6 L/kg) x (50 kg) x (4 ng/mL) = 1200 . . . 1200 what?
  (10^3 mL/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

• LEO GER (CYP 450)
  • Oxidize substrate (lose e\textsuperscript{–})
  • Reduce electrophile (gain e\textsuperscript{–})
  • Cyclical oxidation co-factor
    • I.e. NADH / NAD\textsuperscript{+}
    • 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

\[
\text{CH}_3\text{CHO} + \text{NADPH} + \text{H}^+ + \text{O}_2 \rightarrow \text{CH}_3\text{CHOH} + \text{NADP}^+ + 2\text{H}_2\text{O}
\]

\[
\text{CH}_3\text{CHO} + \text{NAD}^+ \rightarrow \text{CH}_3\text{CHOH} + \text{NADH} + \text{H}^+
\]

**Alcohol Dehydrogenase**

---

PHASE II (SYNTHETIC)

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

---

CYP 450 INTERACTIONS

### CYP 1A2

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

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>broccoli &amp; brussel sprouts</td>
<td>fluvoxamine, ciprofloxacin</td>
</tr>
<tr>
<td>cigarettes, char-grilled meat, insulin, modafinil, omeprazole</td>
<td>amiodarone, cimetidine, clarithromycin, interferon, ticlopidine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
</tr>
<tr>
<td>Carvedilol</td>
</tr>
<tr>
<td>Clonazepam</td>
</tr>
<tr>
<td>Theophylline</td>
</tr>
<tr>
<td>R-warfarin</td>
</tr>
<tr>
<td>APAP</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
</tbody>
</table>

### CYP 2C9

Most abundant CYP2C

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>rifampin, secobarbital, St. John’s Wort</td>
<td>fluconazole, amiodarone, fluvoxamine, isoniazid, lovastatin, sertraline, sulfamethoxazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID’s</td>
</tr>
<tr>
<td>S-warfarin</td>
</tr>
<tr>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>Phenotoin</td>
</tr>
<tr>
<td>ARBs</td>
</tr>
</tbody>
</table>

### CYP 2C19

Absent 20% Asians “PPIs & Seizures”

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine, prednisone, rifampicin, St. John’s Wort</td>
<td>omeprazole, cimetidine, fluoxetine, indomethacin, ketoconazole, modafinil, oxcarbazepine, ticlopidine, topiramate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Phenotoin</td>
</tr>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Omeprazole</td>
</tr>
<tr>
<td>R-warfarin</td>
</tr>
<tr>
<td>Carvedilol</td>
</tr>
</tbody>
</table>
**CYP 2D6**

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dexamethasone, rifampin</td>
</tr>
<tr>
<td></td>
<td><strong>bupropion, fluoxetine, paroxetine, quinidine, sertraline, duloxetine, amiodarone, cimetidine, citalopram, cocaine, doxorubicin, h₁ antagonists, methadone, metoclopramide, ritonavir, ticlopidine</strong></td>
</tr>
</tbody>
</table>

**Substrates**
- β-blockers
- Codeine
- Tamoxifen
- TCAs, SSRIs
- Haloperidol

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

**CYP 2E1**

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanol (chronic), fomepizole, isoniazid, phenobarbital, phenytoin, cigarette smoke</td>
<td>disulfiram, diethyl-dithiocarbamate, ethanol (acute), fomepizole</td>
</tr>
</tbody>
</table>

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

**Toxications**
- Acetaminophen, ifosfamide, acrylonitrile, CCl₄, aniline, benzene, dichloromethane, vinyl chloride

**CYP 3A4**

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine, efavirenz, modafinil, glucocorticoids, oxcarbazepine, phenobarbital, phenytoin, rifampin, st. john’s wort</td>
<td>protease inhibitors, clarithromycin, ketoconazole, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, ciprofloxacin, fluvoxamine, starfruit</td>
</tr>
</tbody>
</table>

**Substrates**
- Benzocaine
- Dapsones
- C₄₅ block
- Haloperidol + APAP
- HIV iavral
- HMG CoA
- Immune
- Macro (≥ A3)
- Methadone
- Modafinil

**Toxications**
- Acetaminophen, aflatoxin
P-GLYCOPROTEIN

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rifampin, st. john’s wort</td>
<td>amiodarone, cyclosporine, ketoconazole, quinidine, ritonavir, tamoxifen, verapamil</td>
</tr>
</tbody>
</table>

Substrates
- Cyclosporine
- Digoxin
- Diltiazem
- Loperamide
- Lovastatin

Toxication

ELIMINATION
ELIMINATION

• Biotransformation, clearance, excretion
• Clearance(ss) = elimination ~ concentration
  • Cl = 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 x 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 x V_d/Cl
MICHAELIS-MENTEN

- “In between” elimination
- Elimination related to concentration
- $k_e = \frac{(V_{\text{max}} \times C)}{(k_m + C)}$
- $V_{\text{max}}$ – 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 ($C \gg k_m$)
  \[ k_e = \frac{(V_{\text{max}} \times C)}{(k_m + C)} = V_{\text{max}} \]
- Fixed amount eliminated per time
- Elimination saturated, capacity limited
- Non-linear; no “half-life”
- Dose $>>$ elimination, no steady state
- Concentration keeps rising with dose

GRAPHS YOU SHOULD KNOW

“ENHANCED” ELIMINATION

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

• Clearance = flow x ER (extraction ratio)
  • ER = (C_{in} – C_{out})/C_{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 x V_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_{total} = Cl_{native} + Cl_{HD}
  • = (90 L/hr) + (12 L/hr) = 102
  • t_{1/2} = (0.693 x 4000 L)/(102 L/hr) =
    • 27.2 hours (better)

WHAT ABOUT CRRTS?

• Cl = (Volume/time of UF) x (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
PHARMACODYNAMICS AND TOXICODYNAMICS

TIME COURSE DRUG ACTION

- Drug (D) - receptor (R) interaction
- \([D] + [R] \leftrightarrow [DR]\)
- \(K_{\text{dissociation}} = [D][R]/[DR]\)
- Effect (E) proportional to occupancy . . .
- \(E = [D]/(K_d+[D])\)
DOSE RESPONSE CURVE

- log-log plot of $E = [D] / (K_d + [D])$
- Sigmoid shaped, linear in middle
- When $E = 50\%$, dose $= K_d$

![Dose Response Curve Diagram]

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 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 \( \uparrow \) dopamine receptors
- GABA \( \downarrow \), NMDA \( \uparrow \) 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
ADVERSE EFFECTS
XENOBIOTIC INTERACTIONS

ADVERSE DRUG EVENTS

• 1.5 million ADE/yr in U.S. (>1/d/pt)
• Predictable
  • Pharmacokinetic/dynamic
• Immunologic
• HIV, 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
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?