PHARMACOKINETICS OF SSRI ANTIDEPRESSANTS

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Selective Serotonin Reuptake Inhibitors (SSRI)

- Citalopram (Celexa, Cipramil, Seropram)
  - Escitalopram (Lexapro)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Venlafaxine (Effexor)
The Bluebird of Happiness long absent from his life, Ned is visited by the Chicken of Depression.
<table>
<thead>
<tr>
<th>Drug</th>
<th># Cases</th>
<th>% Case</th>
<th>Mode</th>
<th>Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Alcohol</td>
<td>2230</td>
<td>76.3</td>
<td>0.12</td>
<td>0.01 - 0.40</td>
<td>gm %</td>
</tr>
<tr>
<td>THC</td>
<td>345</td>
<td>12.0</td>
<td>0.001</td>
<td>&lt;0.001 - 0.026</td>
<td>mg/L</td>
</tr>
<tr>
<td>THC-Acid</td>
<td>442</td>
<td>15.0</td>
<td>0.024</td>
<td>0.002 - 0.280</td>
<td>mg/L</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>108</td>
<td>3.7</td>
<td>0.038</td>
<td>0.020 - 0.672</td>
<td>mg/L</td>
</tr>
<tr>
<td>Diazepam</td>
<td>79</td>
<td>2.7</td>
<td>0.39</td>
<td>0.020 - 1.70</td>
<td>mg/L</td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>91</td>
<td>3.1</td>
<td>0.16</td>
<td>0.050 - 2.10</td>
<td>mg/L</td>
</tr>
<tr>
<td>Cocaine</td>
<td>31</td>
<td>1.1</td>
<td>0.005</td>
<td>0.002 - 0.071</td>
<td>mg/L</td>
</tr>
<tr>
<td>Benzoylecgonine</td>
<td>79</td>
<td>2.7</td>
<td>0.16</td>
<td>&lt;0.100 - 3.2</td>
<td>mg/L</td>
</tr>
<tr>
<td>Butalbital</td>
<td>71</td>
<td>2.4</td>
<td>1.0</td>
<td>0.500 - 38.9</td>
<td>mg/L</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>44</td>
<td>1.5</td>
<td>0.020</td>
<td>0.020 - 202</td>
<td>mg/L</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>40</td>
<td>1.4</td>
<td>0.067</td>
<td>0.024 - &gt;0.500</td>
<td>mg/L</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>36</td>
<td>1.2</td>
<td>0.020</td>
<td>1.0 - 30.0</td>
<td>mg/L</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>38</td>
<td>1.3</td>
<td>0.020</td>
<td>2.1 - 50.0</td>
<td>mg/L</td>
</tr>
<tr>
<td>Phencyclidine [PCP]</td>
<td>37</td>
<td>1.3</td>
<td>0.017</td>
<td>0.013 - 0.089</td>
<td>mg/L</td>
</tr>
<tr>
<td>Morphine</td>
<td>32</td>
<td>1.1</td>
<td>0.030</td>
<td>0.020 - &gt;0.500</td>
<td>mg/L</td>
</tr>
</tbody>
</table>
Trazodone/Olanzapine/Paroxetine in Blood Extract – DB-5
### Toxicology Findings, 43 yr Woman:

<table>
<thead>
<tr>
<th>Drug</th>
<th>blood, mg/L</th>
<th>Liver, mg/Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>1.2</td>
<td>12</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.7</td>
<td>40</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>0.6</td>
<td>26</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>1.4</td>
<td>36</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>&lt;.1</td>
<td>4</td>
</tr>
<tr>
<td>Promethazine</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Doxylamine</td>
<td>0.09</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Antidepressant Drugs: Pharmacokinetic Consideration

- Large Apparent volume of distribution
- Chiral drugs
- Active metabolites
- Biotransformation
  - Interactions with CYP450 isoenzymes
Dosage → Plasma Concentration → Site of Action → Effects

Pharmacokinetics

Pharmacodynamics
ABSORPTION → Free Drug → EXCRETION

Bound Drug ↔ Free Drug

BIOTRANSFORMATION

SYSTEMIC CIRCULATION

LOCUS OF ACTION
“RECEPTORS”
Bound ↔ Free

TISSUE RESERVOIRS
Free ↔ Bound
LOCUS OF ACTION
“RECEPTORS”
Bound ↔ Free

TISSUE RESERVOIRS
Free ↔ Bound

ABSORPTION

Free Drug

Bound Drug

EXCRETION

BIOTRANSFORMATION

SYSTEMIC CIRCULATION

$K_A$

$K_M$

$K_E$
Pharmacokinetic Data

- Bioavailability (%)
- Volume of distribution (L/Kg)
- Bound in plasma (%)
- Distribution Ratio of [plasma]/[blood]
- Plasma half-life (hr)
- Clearance (mL/min/Kg)
- Urinary excretion (%)
Pharmacokinetic Data

- Single dose peak plasma concentration
- Effective steady state plasma concentration
- Toxic plasma concentration
- Life threatening or lethal blood concentration
Bioavailability

Dose → Destroyed in gut → Not absorbed → Destroyed by gut wall → Destroyed by liver → to systemic circulation
Bioavailability

Definition: the fraction of the administered dose reaching the systemic circulation

for i.v.: 100%
for non i.v.: ranges from 0 to 100%

e.g. lidocaine bioavailability 35% due to destruction in gastric acid and liver metabolism

First Pass Effect
Bioavailability = \frac{(AUC) \text{ Oral}}{(AUC) \text{ IV}}
Drugs appear to distribute in the body as if it were a single compartment. The magnitude of the drug’s distribution is given by the apparent volume of distribution ($V_d$).

$$V_d = \frac{\text{Amount of drug in body}}{\text{Concentration in Plasma}}$$

$$V_d = \frac{\text{Dose}}{C_0}$$
Drug concentration in beaker:

Dose = 10 mg  
Cp₀ = 20 mg/L  
Apparent Volume = 500 ml

With charcoal in beaker:

Dose = 10 mg  
Cp₀ = 2 mg/L  
Apparent Volume = 5000 ml
Gradient Between Drug in Blood and Drug in Other Tissues & Fluids

Vd = 1 L/Kg, in 70 Kg man = 70L
If 70mg dose, then $\frac{70mg}{70L/Kg} = 1 \text{ mg/L in blood}$

Distribution

Total drug in blood/total drug in body tissues = $4mg/66mg$

Vd = 10 L/Kg, in 70 Kg man = 700L
If 70mg dose, then $\frac{70mg}{700L/Kg} = 0.1 \text{ mg/L in blood}$

Distribution

Total drug in blood/total drug body tissues = $0.4mg/69.6mg$
Examples of apparent Vd’s for some drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>L/Kg</th>
<th>L/70 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>0.16</td>
<td>11.2</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.63</td>
<td>44.1</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.55</td>
<td>38.5</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2.4</td>
<td>168</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7</td>
<td>490</td>
</tr>
</tbody>
</table>
Hemodialysis

- Rate of toxicant removal related to:
  - Blood flow through dialyzer
  - Dialysate flow rate
  - Drug solubility
  - Permeability of membranes, surface >2M²

- Disadvantages:
  - Infections
  - Blood clots, hematomas
  - Complex apparatus, skill personnel
Dialysis Clearance

- **Dialysis clearance** $= E \times B \times S$
- **Where**
  - $E = \text{extraction ratio} = \frac{C_a - C_v}{C_a}$
    - Where; $C_a$ is concentration of toxicant in arterial blood
    - $C_v$ is concentration of toxicant in venous blood
  - $B = \text{blood flow} (300 \text{ mL/min})$
  - $S = \text{serum factor} (1 - \text{hematocrit})$
Hemodialysis Pharmacokinetics

- Dialyzer flow rate, 300 mL/min
- If Extraction ratio = 1, to totally clear blood (5000 mL) of agent where;
  - \( Ke = \frac{300 \text{ mL/min}}{5000 \text{ mL}} \)
  - \( Ke = 0.06/\text{min} \) (~6%)
  - \( T_{1/2} = \frac{0.0693}{0.06/\text{min}} = 11.6 \text{ min} \)
  - Total removal = 5 x \( T_{1/2} = 58 \text{ min} \)
Hemodialysis Pharmacokinetics
Clearance of Methanol

- Dialyzer flow rate, 300 mL/min
- If Extraction ratio = 1, to totally clear blood (5000 mL) of agent where;
  - Vd = 0.6L/Kg, 70Kg man
  - Ke = 300 mL/min /42000 mL
  - Ke = 0.007/min (~0.7%)
  - T1/2 = 0.0693 / 0.007/ min = 99min
  - Total removal = 5 x T1/2 = 495 min (~8 hours)
Hemodialysis Pharmacokinetics
Clearance of Phenytoin

- Dialyzer flow rate, 300 mL/min
- If Extraction ratio = 1, to totally clear blood (5000 mL) of agent where;
  - $V_d = 0.8 \text{L/Kg}$, 70Kg man
  - $K_e = \frac{300 \text{ mL/min}}{56000 \text{ mL}}$
  - $K_e = 0.005/\text{min}$ (~0.5%)
  - $T_{1/2} = \frac{0.0693}{0.005/\text{min}} = 138\text{min}$
  - Total removal = $5 \times T_{1/2} = 690 \text{ min} (~11.5 \text{ hr})$
Hemodialysis Pharmacokinetics
Clearance of Amitriptyline

- Dialyzer flow rate, 300 mL/min
- If Extraction ratio = 1, to totally clear blood (5000 mL) of agent where;
  - $V_d = 10L/Kg, \text{70Kg man}$
  - $Ke = \frac{300 \text{ mL/min}}{700,000 \text{ mL (700L)}}$
  - $Ke = 0.0004/\text{min (}\sim 0.04\%\)$
  - $T_{1/2} = \frac{0.0693}{0.0004/ \text{min}} = 173\text{min (}\sim 2.9 \text{ hr}\)$
  - Total removal = 5 x $T_{1/2} = 866 \text{ min (}\sim 14.4 \text{ hr}\)$
Hemodialysis Pharmacokinetics

Clearance of Fluoxetine

- Dialyzer flow rate, 300 mL/min
- If Extraction ratio = 1, to totally clear blood (5000 mL) of agent where;
  - Vd = 30L/Kg, 70Kg man
  - Ke = 300 mL/min /2,100,000 mL (2,100L)
  - Ke = 0.00014/min (~0.014%)
  - T1/2 = 0.0693 / 0.00014/ min = 495min (~8.3 hr)
  - Total removal = 5 x T1/2 = 2,475 min (~41.25 hr)
LOCUS OF ACTION
“RECEPTORS”
Bound ↔ Free

TISSUE RESERVOIRS
Free ↔ Bound

IV injection

Free Drug

Bound Drug

K_E

K_M

SYSTEMIC CIRCULATION

BIOTRANSFORMATION

EXCRETION
First Order Elimination

dC/dt related C

\[ \frac{dC}{dt} = -kC \]

\[ C_t = C_0 \cdot e^{-K_E t} \]

\[ \ln C_t = \ln C_0 - K_E t \]

\[ \log C_t = \log C_0 - \frac{K_E t}{2.303} \]

\[ y = b - mx \]
Plasma Concentration Profile after a Single I.V. Injection
First Order Elimination

\[
\log C_t = \log C_0 - K_e t / 2.303
\]
Plasma Elimination Rate Constant

$K_E$ is the fraction of drug continuously removed from plasma (blood) per unit time (hr).

Thus; if $K_E = -0.25/\text{hr}$, the plasma drug concentration is continuously declining by ~25%
Plasma Elimination Rate Constant

\[ K_E = \text{the sum of all rate processes that remove the drug from plasma.} \]

\[ K_E = K_{M1} + K_{M2} + K_U + K_{\text{others}} \]

Where; \( K_{M1} = \text{rate of formation of metabolite 1} \)

\( K_{M2} = \text{rate of formation of metabolite 2} \)

\( K_U = \text{rate of urinary excretion} \)

\( K_{\text{others}} = \text{rate of other processes, ex sweat,} \)
Fluvoxamine Metabolism

Overmars et al European J Drug Pharmacok 8:269-280, 1983
Elimination of drugs from the body

KIDNEY
- filtration
- secretion
  (reabsorption)

LIVER
- metabolism
- secretion

LUNGS
- exhalation

OTHERS
- mother's milk
- sweat, saliva etc.
The **plasma half-life** is the *time* for the plasma concentration to decline to half the original concentration.

\[
\ln C_t = \ln C_0 - K_E t
\]

When: \(\ln C_t = \ln C_{t_{1/2}}\)

\[
\ln C_0 = \ln C_0
\]

\[
t = t_{1/2}
\]

\[
T_{1/2} = 0.693/K_E
\]
Plasma Half-Life

Log Plasma Concentration

Time

Cp

Cp/2

$C_p/2 = 4 \text{ hrs}$

$t_1$

$t_{1/2} = 4 \text{ hrs}$

$t_2$
First Order Elimination

- **Clearance**: volume of plasma cleared of drug per unit time.

\[
\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}
\]
Rate of elimination = $K_E \times$ Amount in body
Rate of elimination = $CL \times [\text{Plasma}]

Therefore,

$$K_E \times \text{Dose} = CL \times [\text{plasma}]$$

$$K_E = \frac{CL}{V_d}$$

$$V_dK_E = CL$$

$$0.693 \frac{V_d}{t_{1/2}} = CL$$
Plasma Clearance

Clearance is used to determine iv infusion rates

\[ C_{ss} \cdot CL = \text{dosing rate} \]

Example, lidocaine

\[ CL = 11 \text{ mL/min/Kg}, \text{ in 70 Kg man } = 0.8 \text{ L/min/Kg} \]

\[ C_{ss} = 3\text{mg/L} \]

Dosing rate = \( 0.8\text{L/min/Kg} \times 3\text{mg/L} = 2.4 \text{ mg/min} \)
BOUND FREE

BOUND FREE

TOXIC RESERVOIRS

SYSTEMIC CIRCULATION

FREE DRUG

BIOTRANSFORMATION

EXCRETION

ABSORPTION

LOCUS OF ACTION

"RECEPTORS"

BOUND FREE

FREE BOUND

FREE Bound

FREE Bound

FREE Bound

FREE Bound

FREE Bound

FREE Bound

FREE Bound
Multiple dosing

- On continuous steady administration of a drug, plasma concentration will rise fast at first then more slowly and reach a plateau, where:

  - rate of administration = rate of elimination

  ie. steady state is reached.
Steady State Concentration
Steady State Plasma Concentrations

- Obtained after dosing for 5 half-lives
- After drug administration is stopped, requires 5 half-lives to decline to zero
Steady State Plasma Concentrations

<table>
<thead>
<tr>
<th>Dose</th>
<th>after dose</th>
<th>after 1 half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st}</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>2\textsuperscript{nd}</td>
<td>150</td>
<td>75</td>
</tr>
<tr>
<td>3\textsuperscript{rd}</td>
<td>175</td>
<td>88</td>
</tr>
<tr>
<td>4\textsuperscript{th}</td>
<td>188</td>
<td>94</td>
</tr>
<tr>
<td>5\textsuperscript{th}</td>
<td>194</td>
<td>97</td>
</tr>
<tr>
<td>6\textsuperscript{th}</td>
<td>197</td>
<td>98</td>
</tr>
</tbody>
</table>
$C_{ss} = \frac{F \text{ (dose)}}{V_d K_e T}$

$C_{ss} = 1.44 \frac{F \text{ (dose)} \ t_{1/2}}{V_d T}$

$C_{ss} =$ Plasma Steady State Concentration  
$F =$ Bioavailability  
$V_d =$ Volume of distribution  
$K_e =$ Plasma elimination rate constant  
$T =$ Dosage interval  
$t_{1/2} =$ Plasma half-life
Pharmacokinetic parameters

- **Volume of distribution**  \[ V = \frac{\text{DOSE}}{C_0} \]

- **Plasma clearance**  \[ \text{Cl} = K_E \cdot V_d \]

- **plasma half-life**  \[ t_{1/2} = \frac{0.693}{K_E} \]

- **Bioavailability**  \[ \frac{(\text{AUC})_x}{(\text{AUC})_{iv}} \]
Variability in Drug Metabolism

Plasma Drug Concentration (mg/L) vs. Daily Dose (mg/kg)
Antidepressant Drugs: Metabolism Consideration

- The metabolism rate for antidepressants can vary due to cytochrome p450 isoenzymes.
- Genetic polymorphisms exist that may classify a person as a “poor metabolizer” of a given p450 enzyme. (i.e. CYP 2D6, CYP 2C19)
- Certain drugs may inhibit the production of a particular enzyme or may compete with an enzyme, thus making an individual a poor metabolizer.
Cytochrome P-450 Cycle

R-OH or epoxide → [P-450 (Fe$^{3+}$)] [RH]

O$_2$ = [P-450 (Fe$^{2+}$)] [RH]

H$_2$O → 2H$^+$

[e- via NADPH or NADH plus a reductase enzyme]

RH substrate → [P-450 (Fe$^{2+}$)] [RH]

O$_2$ → [P-450 (Fe$^{2+}$)] [RH]

[e- via NADPH plus a reductase enzyme]

O$_2$ → [P-450 (Fe$^{2+}$)] [RH]

R-OH or epoxide
Cytochrome P-450: Oxidative

- Structural diversity due to
  - Nonspecificity
  - Isozymes - multiple forms of an enzyme
- Enzymes are “inducible” by various chemicals
- Exposure increases the rate of enzyme production
Cytochrome P-450: Oxidative

- Isozymes differ in protein structure
  - Different amino acid sequences
  - Produce different 3-D structures
  - Drug bound to the protein portion

- Remember:
  - *All activated oxygen chemistry occurs at the iron center heme with oxygen transfer to the protein bound substrate*
Polymorphism in Clinical Pharmacology

- **Drug metabolism enzymes**
  - Cytochrome P450's (CYP)
  - NAD(p)H quinone oxidoreductase
  - N-acetyl transferase (NAT)
  - Thiopurine methyltransferase (TPMT)

- **Receptor proteins**
  - $\alpha_2$-Adrenergic receptor
  - Dopamine D3-receptor
Genetic Polymorphism

- Structural variations of a gene (Allele)
  Mendelian inheritance
  - **Homozygous:** Two common or two variant alleles
  - **Heterozygous:** One common and one variant allele
  - **Recessive:** Must be homozygous to reveal phenotype
  - **Dominant:** Heterozygous genotype displays variant phenotype
Mechanisms of polymorphism

- Single nucleotide
  - Coding region
  - Non-coding region
    - Regulatory sequences
    - Intron
- Gene deletion, duplication
Cytochrome P450 Nomenclature

- CYP’s that have 40% or greater sequence homology are classified as the same family.
- Enzymes with 55% or greater sequence homology are classified in the same subfamily.
- CYP2D6 is the abbreviation for the CYP in family 2, subfamily D, gene product 6.
Nomenclature

Cytochrome P450 2D6 *4

Superfamily

Family

Subfamily

Isoenzyme

Allele Variant
Hepatic Cytochrome P450 Content

1A2: 18%
2A6: 5%
2B6: 1%
3A: 40%
2C: 24%
2D6: 3%
'E1: 9%
Cytochrome P450 Isoenzymes

- It has been reported that for drugs that undergo oxidative biotransformation
  - 50% metabolized by CYP 3A3/4
  - 30% metabolized by CYP 2D6
  - 10% metabolized by CYP 2C9/10
  - 4% metabolized by CYP 1A2
  - 2% metabolized by CYP 2C19
  - 2% metabolized by CYP 2E1
Cytochrome P450 2D6

- Polymorphism – none or have less than normal amounts
  - 5-10% of Caucasians – poor metabolizers
  - ~1% of Asian – poor metabolizers
- Many important hydroxylation reactions
  - antidepressants, antipsychotics, analgesics, & cardiovascular drugs
- 2D6 can be inhibited by drugs
  - Not necessary for drug to be substrate to inhibit P450
- Autoinhibition
<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>SSRI</td>
</tr>
<tr>
<td>TCA’s</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Codeine</td>
<td>Chlorpromazine, Cocaine</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Methadone, Doxorubicin</td>
</tr>
<tr>
<td>Dextromethophan</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Encainide</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Flecainide</td>
<td></td>
</tr>
</tbody>
</table>
SSRI Inhibitors
Cytochrome P450 2D6

- Weak to Moderate Inhibitors
  - Citalopram
  - Duloxetine
  - Fluvoxamine
  - Sertraline
- Potent Inhibitors
  - Fluoxetine
  - Norfluoxetine
  - Paroxetine
## Cytochrome P450 3A4

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Antidepressants-SSRIs</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td></td>
</tr>
<tr>
<td>Omeprezole</td>
<td></td>
</tr>
</tbody>
</table>
Inducers of Cytochrome P450 3A4

- Barbiturates
- Carbamazepine
- Glucocorticoids
- Phenytoin
- Rifampin
- St. John’s wort
SSRI Inhibitors
Cytochrome P450 3A4

- **Weak Inhibitor**
  - Citalpram
  - Fluoxetine
  - Paroxetine
  - Sertraline

- **Potent Inhibitor**
  - Norfluoxetine
  - Fluvoxamine
Michaelis-Menten Kinetics

\[ V = V_{\text{max}} \left( \frac{[S]}{[S] + K_m} \right) \]

- If \([S] \gg K_m\), \(V = V_{\text{max}}\)
- If \(K_m \gg [S]\), \(V = \text{constant} [S]\)
Reciprocal Michaelis-Menten

\[
\frac{1}{V} = \frac{1}{V_{\text{max}}} + \frac{K_m}{V_{\text{max}}} \times \frac{1}{[S]}
\]

- **Intercept on y-axis**: \(\frac{1}{V_{\text{max}}}\)
- **Slope**: \(\frac{K_m}{V_{\text{max}}}\)
- **Intercept on x-axis**: \(-\frac{1}{K_m}\)

**Graph**: The graph shows a line with the intercept on the y-axis at \(\frac{1}{V}\) and the intercept on the x-axis at \(-\frac{1}{K_m}\). The slope of the line is \(\frac{K_m}{V_{\text{max}}}\).
### Competitive Enzyme Inhibition

\[
1/V = 1/V_{\text{max}} + \frac{K_m}{V_{\text{max}}} (1 + 1/K_1)(1/[S])
\]

Where, \(K_1\) is the dissociation constant of the enzyme-inhibitor complex

In the presence of an inhibitor, the slope increases by the factor \((1 + 1/K_1)\)

\(K_m\) is increased

\(V_{\text{max}}\) is unaltered
Competitive Enzyme Inhibition

1/V vs 1/[S]

Competitive inhibitor

No inhibitor present
Factors Complicating Interpretation of Postmortem Blood Concentrations

- Large individual variations in pharmacokinetic parameters in therapeutic situations
- Alterations in pharmacokinetics in overdose
  - Saturation of biotransformation & elimination
  - Non-equilibrium distribution
- “postmortem release” of tissue bound drugs into blood after death

Postmortem Blood to Calculate Dose

If $V_d$ is low, then $V_d = \frac{Dose}{C_0}$

If $V_d$ is high, then $C_b V_d$ does not $= Dose$
Selective Serotonin Reuptake Inhibitors (SSRI)

- Citalopram (Celexa, Cipramil, Seropram)
  - Escitalopram (Lexapro®)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Venlafaxine (Effexor)
Variability in Pharmacokinetics

![Graph showing variability in plasma drug concentration vs. daily dose](image-url)
SSRI Metabolism

- Inhibit metabolism of other drugs
- Autoinhibition:
  - inhibit their own metabolism
  - non-linear relationship between dose and blood concentration
  - increase blood half-life with increasing doses
SSRI’s That Exhibit Autoinhibition

- Fluoxetine & norfluoxetine
- Fluvoxamine
- Paroxetine
Citalopram
Citalopram

- Dosage: 20-60 mg/day
- Bioavailability: 80%
- Fb: 0.80
- Time to Peak: ~4 hr
- Vd: 12-16 L/kg
- $t_{\frac{1}{2}}$: 25-35 hr
- Time to Steady State: 6-7 days
Citalopram

- Biotransformation
  - Desmethycitalopram CYP3A4 / CYP2D6 / CYP 2C19
  - Didesmethycitalopram, CYP 2D6
- Active Metabolite:
  - Desmethycitalopram (25-50% of parent)
  - Didesmethycitalopram (10% of Parent)
- % excreted in urine:
  - citalopram 12%
  - desmethycitalopram 5%
Citalopram

- Very weak inhibitor
  - CYP 3A4
  - CYP 2B6
  - CYP 2C9
  - CYP 2D6
  - CYP 2C19

- Elderly, increased half-life
- Hepatic disease – little effect
- Renal disease – little effect
CITALOPRAM METABOLISM

desmethylcitalopram

N-didesmethylcitalopram
Citalopram & Quetiapine

Abundance

Alprapruline

Citalopram

Quetiapine Metabolite

Quetiapine
Citalopam & Others

- Isid
- Caffeine
- Norfluoxetine
- Tramadol
- O-Desmethylramadrol
- Nortriptyline
- Diazepam
- Citalopram
Citalopram Serum Values

- Single- and multiple-doses both produce linear and dose proportional effects within the 10-60 mg/day prescription.

- Therapeutic value
  - citalopram 50-100 ng/mL
  - desmethycitalopram 15-40 ng/mL

- Toxic Concentration > 1,000 (?)
Citalopram Isomers

- “S” and “R” isomers (racemic mixture)
- “S” isomer 2-4 times SSRI than “R”
Citalopram Enantiomers in Femoral Blood, 53 Postmortem Cases

- **Citalopram**
  - Mean S isomer 1.53 ug/mL, SD = 3.57
  - Mean R isomer 1.72 ug/mL, SD = 3.58
  - S/R = 0.67, SD 0.25

- **Desmethylcitalopram**
  - Mean S isomer 0.14 ug/mL, SD = 0.21
  - Mean R isomer 0.20 ug/mL, SD = 0.22
  - S/R = 0.68, SD 0.20

*Holmgren et al J. Anal. Toxicol. 26:94-104, 2004*
Escitalopram

- “S” isomer citalopram)
- 10 mg = 20-40 mg citalopram
Escitalopram CYP 450

- R & S isomers metabolized by same P450
- Substrate:
  - CYP 2C19
  - CYP 3A4
  - CYP 2C19
- Weak inhibitor:
  - CYP 2D6
Duloxetine
Duloxetine

- Dosage: 40-120 mg/day
- Bioavailability: 95%
- Fb: 95%
- Time to Peak: ~4 hr
- Vd: Mean 27 L/Kg (13-50 L/kg)
- $t_{1/2}$: 6-19 hr
- Time to Steady State: 3-5 days
Duloxetine Elimination

- Biotransformation
  - Extensive ring hydroxylation
  - O-Methylation
  - Glucuronide & sulfate conjugation
- Plasma metabolites as glucuronides:
  - 4-hydroxy-duloxetine
  - 5,6-hydroxy-duloxetine
  - 6-hydroxy-5-methoxy duloxetine
  - 4,6-dihydroxy-duloxetine
- Radioactivity excreted in urine: 72% in 13 days
- Radioactivity excreted in feces: 18% in 13 days
Duloxetine Metabolism

- **Substrate:**
  - CYP 2D6
  - CYP 1A2

- Bioavailability reduced by 1/3 in smokers

- Elderly, no significant change in half-life

- Moderate inhibitor
  - CYP 2D6
Duloxetine Plasma Metabolites

Lanz et al. Drug Metab. Dispos. 31:1142,2003

6-hydroxy Catechol

4,6-hydroxy

5-hydroxy-6-methoxy
Duloxetine Urine Metabolites

11 hydroxylated and hydroxy-methoxy metabolites
Excreted as glucuronide and sulfate conjugates

10 – 16%

13 – 21%
Duloxetine Serum Steady-State Trough Values

- Twelve healthy adult men
- Dose 20 mg bid
  - 12ng/mL (2 – 12ng/mL)
- Dose 30 mg bid
  - 20 ng/mL (10 – 48 ng/mL)
- Dose 40 mg bid
  - 30 ng/mL (12– 40 ng/mL)

Generally trough serum values > 5 ng/mL predicts sustained inhibition of 5-HT reuptake.

Fluoxetine
Fluoxetine

- Dosage: 20-80 mg/day
- Fb: 0.94
- Time to Peak: 6-8 hr
- Vd: 20-42 L/kg
- Time to Steady State: 1 week – month
- % excreted as parent in urine: <10%
Fluoxetine Stereoisomers

Similar SSRI activity
Norfluoxetine Stereoisomers

S >>>>> R in SSRI activity
FLUOXETINE METABOLISM

- Biotransformation to norfluoxetine is mediated by CYP 2D6
- 7% of population reduced CYP 2D6 activity
  - S isomer metabolized slower to norfluoxetine, results in higher Flu/norflu
  - R isomer normal rate
- At steady-state concentration of the 4 parent-metabolite isomers equal
- No pharmacological difference
Fluoxetine CYP 450

- **Substrate:**
  - CYP1A2
  - CYP 2B6
  - CYP 2C8/9
  - CYP 2C19
  - CYP 2D6
  - CYP 2E1
  - CYP 3A4
Fluoxetine CYP 450

- Moderate to severe inhibitor:
  - CYP 1A2
  - CYP 2B6
  - CYP 2C8/9
  - CYP 2C19
  - CYP 2D6
  - CYP 3A/4

- Norfluoxetine: Inhibitor of 3A3/4 (potent)
FLUOXETINE METABOLISM

Trifluoromethylphenol

Norfluoxetine
Fluoxetine / Norfluoxetine
Fluoxetine Half-life

- $t_{1/2}$: 24-72 hr (dose dependent)
  - short term doses 1-3 days
  - long term doses 4-6 days

- $t_{1/2}$: norfluoxetine (1st order)
  - short term doses 4-16 days
  - long term doses 4-16 days
FLUOXETINE METABOLISM

- Half-life increased with hepatic disease
- Half-life not influenced by
  - Decreased renal function
  - Elderly
  - Pediatric patients
Fluoxetine Serum Values

- Single 40 mg dose = 15-55 ng/mL
- 40 mg/day for one week
  - Fluoxetine 91 – 300 ng/mL
  - Norfluoxetine 72 – 260 ng/mL
- 40 mg/day for one month
  - Fluoxetine 47 – 470 ng/mL
  - Norfluoxetine 52 – 450 ng/mL
Fluoxetine Serum Values

- Large variation in peak and trough concentrations dependent upon
  - Dose
  - Dosage regiment
  - Co-administration of other drugs

- Therapeutic values
  - fluoxetine, ~100 - 500 ng/mL
  - norfluoxetine, ~100 - 450 ng/mL

- Toxic Concentrations
  - Fluoxetine >1,500 ng/mL (?)
Desipramine

- **Dosage:** 25-300 mg/day
- **Fb:** 0.95
- **Time to Peak:** 3-6 hr
- **Vd:** 22-59 L/kg
- **t \( \frac{1}{2} \):** 12-54 hr
- **Time to Steady State:** 2-8 days
DESIPRAMINE METABOLISM

iminodibenzyl

nordesipramine

CYP3A4

10-OH-desipramine

CYP2D6

2-OH-desipramine
Metabolism of Desipramine

- Mediated by CYP1A2, CYP3A4, CYP2C19
  - Desipramine $\rightarrow$ 10-OH-Desipramine

- Mediated by CYP2D6
  - Desipramine $\rightarrow$ 2-OH-Desipramine
Fluoxetine/Desipramine

- Chronic administration
  - 20 mg/day fluoxetine
  - 50 mg/day desipramine
- Desipramine plasma values increased 4X with concomitant fluoxetine
- Desipramine plasma values still elevated 3 weeks after fluoxetine discontinued
Fluvoxamine
Fluvoxamine

- **Dosage:** 100-200 mg/day
- **Fb:** 0.77
- **Time to Peak:** 2-8 hr
- **Vd:** 25 L/kg
- **$t_{1/2}$:** 8-24 hr (dose dependent >200mg)
- **Time to Steady State:** 2-4 days
Fluvoxamine Elimination

- Extensively biotransformed
  - Oxidation, deamination
  - N-O cleavage
  - N-acetylated
- % excreted as parent in urine: ~3%
- Therapeutic Concentration
  - ~200 ng/mL
- Toxic Concentration
  - >2,500 ng/mL (?)
Fluvoxamine CYP 450

- **Substrate:**
  - CYP1A2
  - CYP 2D6

- **Moderate to Severe Inhibitor:**
  - CYP 1A2
  - CYP 2B6
  - CYP 2C8/9
  - CYP 2C19
  - CYP 2D6
  - CYP 3A/4
Fluvoxamine Metabolism

Overmars et al European J Drug Pharmacok 8:269-280, 1983
Fluvoxamine Metabolism, cont.
Fluvoxamine / Meperidine / Trazodone
Fluvoxamine Serum Values

- Single dose 100 mg
  - Peak 31-87 ng/mL
- Therapeutic Concentration
  - ~200 ng/mL
- Toxic Concentration
  - >2,500 ng/mL (?)
Paroxetine
Paroxetine

- Dosage: 10-50 mg/day
- Fb: 0.95
- Time to Peak: 3-8 hr
- Vd: 5-28 L/kg
- Time to Steady State: ~ 1 week
Paroxetine Elimination

- CYP 2D6 Polymorphism
- Extensively biotransformed
  - ring oxidative cleavage
- $t_{1/2}$: 7-37 hr (dose dependent)
  - fast met, $\sim$ 16 hr
  - slow met (7% population), $\sim$ 41 hr
- Parent excreted in urine: <1%
Paroxetine & CYP 450

Substrate: **CYP2D6**

Moderate to serve Inhibitor

- CYP1A2
- CYP 2B6
- CYP 2C8/9
- CYP 2C19
- CYP 2D6
- CYP 3A/4
PAROXETINE METABOLISM
Paroxetine / Amitriptyline

- Paroxetine
- Amitriptyline
- Nortriptyline
- Alphaprodine
- Paroxetine
Paroxetine / Methadone

TIC: 6024.D

Abundance

Time-->
Paroxetine Serum Values

- Single 20 mg dose peak
  - 1 – 33 ng/mL
- 30mg/day, steady-state (15 subjects)*
  - Peak, average 62 ng/mL
  - Trough, average 31 ng/mL
- Toxic Concentration
  - >300 ng/mL (?)

Sertraline
Sertraline

- Dosage: 50-200 mg/day
- Fb: 0.99
- Time to Peak: 6-8 hr
- Vd: 70 L/kg
- Half-life:
  - Sertraline 22-36 hr
  - Norsertraline 60 –70 hr
- Time to Steady State: 4-6 days
Sertraline Elimination

- Biotransformed
  - N-dealkylation
  - Ring hydroxylation
- Active Metabolite: norsertraline (20% of parent)
- Metabolism decreased
  - Hepatic disease
  - Elderly patients
- % of parent excreted in urine: <0.2%
Sertraline & CYP450 Isozymes

- Moderate Inhibitor at high doses
  - CYP 2C19
  - CYP 3A3
  - CYP 3A4
  - CYP 2B6
  - CYP 2C19

- Weak Inhibitor
  - CYP 2C8/9
  - CYP 1A2
  - CYP 2D6
SERTRALINE METABOLISM

H -N-CH$_3$

\[\text{Norsertraline}\]

\[\text{CYP 3A4}\]

\[\text{Norsertraline}\]
Sertraline in Blood Extract DB-5

Abundance

Time -->

TIC: 6476.4

Istd
Phthalate
Sertraline
Norsertaline

10.00 10.50 11.00 11.50 12.00 12.50 13.00 13.50 14.00 14.50
Methadone / Sertraline in Blood Extract DB-5

Abundance

Time

Alphaprodine, IS
methadone
norsertraline
sertraline

TIC: 1507.D
Sertraline Serum Values

- **Single dose average peak**
  - 50 mg dose, ~10 ng/mL
  - 100 mg dose, 16 ng/mL
  - 200 mg dose, 56 ng/mL

- **Steady State average (range)**
  - 50 mg dose, 32 ng/mL (20 – 48)
  - 100 mg dose, 91 ng/mL (40 – 187)
  - 200 mg dose, 206 ng/mL (99 – 309)
Risperidone Metabolism

2-Hydroxyrisperidone

9-Hydroxyrisperidone
Risperidone Metabolism

9-HO-risperidone, equipotent
Risperidone Pharmacokinetics
CYP2D6 Polymorphism

- Plasma half-life
  - *Slow*
    - Risperidone ~20 hr
    - 9-HO-risperidone ~30 hr
  - *Fast*
    - Risperidone ~3 hr
    - 9-HO-risperidone ~21 hr
Sertraline & Risperidone

- Patients receiving 4 – 6mg/day, at 2 months average plasma concentration
  - Risperidone + 9-hydroxy risperidone
    - 53 +/- 12 ng/mL
- Sertraline added 50mg/day after 2 months
  - Risperidone + 9-hydroxy risperidone
    - 55 +/- 10 ng/mL
  - Sertraline range 22 – 43 ng/mL

Spina et al Ther Drug Monit 26:386, 2004
Venlafaxine
Venlafaxine

- **Dosage:** 75-225 mg/day
- **Fb:** 0.99
- **Time to Peak:** 2-4 hr
- **Vd:** 4-12 L/kg
- $t^{1/2}$: venlafaxine 3-7 hr
  - o-methyl metabolite 9-13 hr
- **Time to Steady State:** 1-3 days
Venlafaxine Elimination

- Biotransformed - polymorphism
  - N-dealkylation
  - O-dealkylation
- Active Metabolite: O-desmethylvenlafaxine
- % excreted in urine:
  - parent, 5%
  - O-methylvenlafaxine, 29-48%
  - N-didesmethylvenlafaxine, 6-19%
  - N-desmethylvenlafaxine, 0.2-8%
Venlafaxine CYP 450

- **Substrate:**
  - CYP 2C8/9
  - CYP 2C19
  - CYP 2D6
  - CYP 3A/4

- **Inhibitor:**
  - CYP 2B6
  - CYP 2D6
  - CYP 3A/4
VENLAFAXINE METABOLISM

N-desmethylvenlafaxine

O-desmethylvenlafaxine

N,N-didesmethylvenlafaxine
Venlafaxine & Metabolites

Venlafaxine
n-desmethylvenlafaxine
o-desmethylvenlafaxine
Met ?
diazepam
nordiazepam
Venlafaxine Steady-State Serum Value

- Steady state 150 mg/day, 50mg tid
  - venlafaxine, peak 194 ng/mL, SD 67 ng/mL
  - venlafaxine, trough 52 ng/mL, SD 38 ng/mL
  - O-desmethyl, peak 313 ng/mL, SD 118 ng/mL
  - O-desmethyl, trough 185 ng/mL, SD 67 ng/mL

- Steady state 150 mg/day, 75mg bid
  - venlafaxine, peak 189 ng/mL, SD 54 ng/mL
  - venlafaxine, trough 56 ng/mL, SD 31 ng/mL
  - O-desmethyl peak 308 ng/mL, SD 121 ng/mL
  - O-desmethyl, trough 194 ng/mL, SD 75 ng/mL

Venlafaxine Serum Value

- Single 50 mg dose average
  - venlafaxine, 70 ng/mL (2.2 hr)
  - O-desmethylvenlafaxine, 106 ng/mL (3.9 hr)

- Toxic concentrations
  - >5,000 ng/mL (?)

- Postmortem blood concentrations
  - Ave. 56 mg/L (6 – 89 mg/L)

R.C. Baselt, *Disposition Toxic Drugs & Chemicals in Man, 6ed, 2002*