Clinical Pharmacology

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Therapeutics: choosing the right drug and dose for the patient
Clinical Toxicology: identifying poisons in clinical and forensic cases
Clinical Drug Trials: testing drugs in man
(Regulatory: Drug choice for nation, hospital & practitioner)
Therapeutics: the right drug and dose for the patient

**Drug & Dose**

Absorption
Distribution
Metabolism
Excretion

**Drug Level**

Target interaction

**Therapeutic response**

Toxicity

Knowable before treatment

- Age, sex, size, history drug response
- Genetics: pharmacokinetics & response
- Disease: elimination & target organs
- Other therapy: Interactions

Knowable during treatment

- Therapeutic drug monitoring
- Drug effect (clinical & laboratory)

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**Dose**

Absorption
Distribution
Metabolism
Excretion

**Drug Level**

Target interaction

**Therapeutic response**

Toxicity

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**Pharmacokinetics**

**Pharmacodynamics**

Absorption
Distribution

Elimination

$V_1$

$E_{MAX}$

50%

Log [Drug]

Log K
Therapeutic Drug Monitoring

- Rationale for TDM: drugs that need measuring and drugs that don’t.
- When and what to measure
- Dose adjustment

Rationale for TDM

Therapeutic Range

Concentration range where efficacy without toxicity may be expected in most patients

Alternatively, ideal may be defined as a “target concentration”
### Rationale for TDM

**Drugs with narrow therapeutic range, where response is difficult to quantify clinically**

**Examples**
- Digoxin
- Anticonvulsant drugs
- Cyclosporin, Sirolimus, Tacrolimus (immunosuppressants: see later)
- Lithium (for bipolar disorder)
- Aminoglycoside antibiotics
- Methotrexate in cancer chemotherapy

### Rationale for TDM

Where drug response can be measured, drug concentration adds little additional information.

**Examples**
- Analgesia with morphine
- Blood pressure response to antihypertensives
- Blood glucose response to antidiabetic drugs
- Infection response to antibiotics
- Coagulation (prothrombin time: INR) response to warfarin
Clinical Indications for TDM

- High pharmacokinetic variability
- Patient non-compliant?
- Failure of absorption?
- Excessive dose for this patient → toxicity?
- Failure of renal or hepatic drug elimination?
- Non-linear pharmacokinetics
- Altered physiological state: pregnancy

When and what to measure

Estimating Target Organ Exposure: Area Under Concentration-Time Curve (AUC)?

AUC at steady state gives best insight into exposure of target tissue over dosage interval

Problem: not clinically practical
Sample at equilibrium: typically, just before next dose ("trough")

Repeated dosing: When to sample

<table>
<thead>
<tr>
<th>Number of t½ since 1st dose</th>
<th>[Drug] % of final steady-state level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>87.5</td>
</tr>
<tr>
<td>4</td>
<td>93.75</td>
</tr>
<tr>
<td>5</td>
<td>96.875</td>
</tr>
</tbody>
</table>

Exceptions:
- Sample immediately:
  - ? toxic
  - ? Compliant
- Sample at specific times:
  - Special situations
Using pharmacokinetic data and drug levels to choose doses

- Loading dose
- Maintenance dose: “linear” pharmacokinetics
- Maintenance dose: “non-linear” kinetics

“Linear” just means that concentrations at any particular time after a dose are proportional to the dose.

**Loading dose**

\[ V_d = \frac{Dose}{C_0} \]

EG: a typical dose of the antibiotic gentamicin for an 80kg patient, to achieve a bacteriocidal peak concentration \( C_0 \) of 5mg/L would be 320mg. That corresponds to an estimated \( V_d \) of 0.8 L/kg (64 litres).

Peak concentration would then be measured, to refine estimate of \( V_d \), for future doses.
Maintenance doses, at equilibrium, linear pharmacokinetics

Dose

Drug in = Drug out
Dose = Elimination

[Drug]
Volume of distribution (Vd)

Elimination

Effect

Why?

Pseudolinearity
Reaction rate $\propto$ [Drug]
If we call [Drug] "C"
This is the same as:
$\delta C/\delta t \propto C_i$
or: $\delta C/\delta t = C_i \cdot k_e$

But:
$\delta C/\delta t \neq$ elimination

How do you determine $k_e$?

Relationship between elimination & C

Dose

C

$V_d$

Elimination

Effect

Elimination = $\delta C/\delta t \cdot V_d$ = maintenance dose

Determining $k_e$

$\delta C/\delta t = C_i \cdot k_e$

$k_e = \frac{\delta C/\delta t}{C_i}$
At 1 hour, \( C_1 = 9 \text{mg/L} \), so \( C \) has fallen by 1mg/L (\( \frac{1}{10}^{th} \)). So, if \( V_d = 64 \text{L} \), you can almost say that 6.4L has been completely cleared of the drug in an hour.

\[ CL = 6.4L/h \]

Relationship between \( k_e \) and clearance: consider a single IV dose.

- **Proportion of total removed in 1 hr**
  - \( CL = \frac{\Delta C_{t=1}}{C_t}V_d \)
  - \( CL = \frac{8C_t}{8t}C_tV_d \)
  - \( k_e \)

\[ CL = k_e \cdot V_d \]

CL is the same for all concentrations

**Units of CL:** L/hr; ml/min

**Dosage Adjustment: Linear Pharmacokinetics**

- **Hallmarks of first order (linear) elimination**

\[ \frac{D_1}{C_{max_1}} = \frac{D_2}{C_{max_2}} = \frac{D_3}{C_{max_3}} \]

**Dose adjustment:** Proportional ("Linear")

\[ \frac{C_1}{D_1} = \frac{C_2}{D_2} = \frac{C_3}{D_3} \]
So, we now have relationships between D, $k_e$, $V_d$, CL and AUC.

Intuitively:
- ↑ D → ↑ AUC
- ↑ CL → ↓ AUC

Area Under Concentration-Time Curve (AUC)

IE
AUC \propto Dose
AUC \approx 1/CL

Disordered Drug Elimination in Clinical Medicine
Example of renal impairment

Examples of drugs with narrow therapeutic range, that are mostly renally eliminated
- Digoxin
- Lithium (for bipolar disorder)
- Aminoglycoside antibiotics
- Methotrexate in cancer chemotherapy
Example: Accumulation of a 100% renally-eliminated drug

Range

CI = 120 ml/min
T_{1/2} = 3 hr

CI = 60 ml/min
T_{1/2} = 6 hr
AUC doubled!

Estimating doses for patients with impaired renal function
Reproduce exposure (AUC) of normals

AUC \propto \text{Dose}
AUC \approx 1/\text{CL}

So: If we knew how much renal drug clearance had fallen, we could estimate total drug clearance, then propose a dose to give the same AUC
**Creatinine clearance: an estimate of renal excretory function**

**Reasoning:** Creatinine is produced at a constant rate by muscle. The amount produced (and excreted) is predictable from age, sex & lean body weight. It is entirely renally excreted.

\[
Cl_{Cr} \text{ (L/hr)} = \frac{\text{amount excreted} \, (\mu\text{Mol/hr})}{\text{serum concentration} \, (\mu\text{Mol/L})}
\]

So, by estimating production and measuring serum creatinine (a cheap, accurate, routine lab test), we can determine \( Cl_{Cr} \), and express it as a proportion of normal.

Then: infer that renal \( Cl_{Drug} \) clearance is proportionally reduced

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### Lithium, ~ 100% renally eliminated

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Impaired Renal Function Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Cl_{Cr} )</td>
<td>120 ml/min</td>
<td>80 ml/min</td>
</tr>
<tr>
<td>Dose</td>
<td>1,800mg/day</td>
<td>1,200mg/day</td>
</tr>
<tr>
<td>([Li^+]_{SS})</td>
<td>1.0mM/L</td>
<td>1.0mM/L</td>
</tr>
</tbody>
</table>

Pathology labs routinely report [Cr] and an approximation of \( Cl_{Cr} \). \( Cl_{Cr} \) is more accurately estimated by Cockcroft-Gault equation.
What about drugs only partly renally excreted?

Example of digoxin

- **Total Digoxin Clearance (175 ml/min)**
- **70% Renal Clearance (125 ml/min), Declines in proportion to Cl\textsubscript{Cr}**
- **30% Non-Renal Clearance (50 ml/min): Does not change**

<table>
<thead>
<tr>
<th>Cl\textsubscript{Cr}</th>
<th>Renal Cl\textsubscript{Digoxin}</th>
<th>Non-renal Cl\textsubscript{Digoxin}</th>
<th>Total Cl\textsubscript{Digoxin}</th>
<th>Dose digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 ml/min</td>
<td>125 ml/min</td>
<td>50 ml/min</td>
<td>175 ml/min</td>
<td>250 µg/day</td>
</tr>
<tr>
<td>80 ml/min</td>
<td>83 ml/min</td>
<td>50 ml/min</td>
<td>133 ml/min</td>
<td>190 µg/day</td>
</tr>
</tbody>
</table>

Dose digoxin: 250 µg/day when Cl\textsubscript{Cr} = 120 ml/min, 190 µg/day when Cl\textsubscript{Cr} = 80 ml/min.

Liver impairment & hepatically eliminated drugs

No quantitative test of liver function is analogous to Cl\textsubscript{Cr}.

Guidelines for dosing of hepatically-eliminated drugs, in patients with hepatic impairment, are drug-specific and imprecise.

Drug levels and clinical/lab tests of drug response help.
"Non-linear" = "Zero Order" = "Saturable" elimination
Elimination of a fixed amount

\[ \Delta C/C_0 \cdot V_d = CL \]
\[ \Delta C/10 \cdot V_d = CL \]
\[ \Delta C/9 \cdot V_d = CL \]
\[ \Delta C/8 \cdot V_d = CL \]
CL changing!

Perhexiline, phenytoin, alcohol

- Longer t½ at higher concentration
- "Concentration-dependent clearance"
- Disproportionate ↑ C with ↑ D

Maintenance Dose adjustment: Less than proportional (iterative)

Drug Interactions through hepatic CYP450 metabolism

**Phase I:**
- oxidation, hydroxylation, deamination, dealkylation, hydrolysis
- increase water solubility and facilitates Phase 2 metabolism

**Phase II:**
- conjugation, mainly to glucuronide or sulphate,
- furthur increases water solubility
**Induction: Examples for Prac**

<table>
<thead>
<tr>
<th>Inducer</th>
<th>NHR</th>
<th>Target</th>
<th>Major Drugs Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>AhR</td>
<td>CYP1A2</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>PXR</td>
<td>CYP3A4</td>
<td>Includes voriconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2C9</td>
<td>Includes voriconazole</td>
</tr>
</tbody>
</table>

**Competitive inhibition: Example for Prac**

| CYP1A2 | Caffeine, clozapine |

**Pharmacogenetics in clinical practice**

- **CYP2C9** and **VKORC1** in warfarin response
- Thiopurine Methyltransferase in azathioprine and mercaptopurine elimination: not discussed here
- HLA-B*5701 in abacavir hypersensitivity: not discussed here
**Warfarin**

Anticoagulant, prevents synthesis of functional clotting factors prothrombin (II), VII, IX & X in liver

Inhibits Vitamin K recycling from KO (inactive) to KH$_2$ (active)

Warfarin elimination
Hepatic CYP2C9, mainly

Vitamin K Epoxide Reductase Complex 1 (VKORC1)

Decarboxy-II, VII, IX, X
Consequences of uncontrolled anticoagulation

Too little
- Blood clots form in circulation, embolise. May be lethal

Too much
- Bleeding: may be lethal in brain or other critical area

What dose does the individual patient need?

During therapy
- Coagulation tests: “prothrombin time”

Before starting?
- Genetic influence on warfarin response

VKORC1: Warfarin Sensitivity

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>Warfarin Sensitivity Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1639 GG</td>
<td>Less sensitive → needs bigger dose</td>
</tr>
<tr>
<td>-1639 GA</td>
<td>Intermediate sensitivity</td>
</tr>
<tr>
<td>-1639 AA</td>
<td>More sensitive → needs smaller dose</td>
</tr>
</tbody>
</table>

CYP2C9: Warfarin Metabolism

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Average Daily Warfarin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1 (wt/wt)</td>
<td>Rapid metaboliser</td>
<td>~ 6 mg</td>
</tr>
<tr>
<td><em>1/</em> (2 or *3)</td>
<td>Intermediate metaboliser</td>
<td>~ 5 mg</td>
</tr>
<tr>
<td>(*2 or *3)</td>
<td>Poor metaboliser</td>
<td>~ 2 mg</td>
</tr>
</tbody>
</table>

*2 or *3: → less efficient enzyme than *1 (wt)

Higashi et al., JAMA 2002;287:1690

Therapeutics vs Poisoning: same concepts

Paracelsus

What is there that is not a poison?
All things are poison and nothing is not a poison.
Only the dose differentiates a poison from a remedy
Examples of Poisoning Syndromes (“Toxidromes”)

Clinician deduces the identity (pharmacological class) of the intoxicant from clinical signs in the patient

**Stimulants** (amphetamines / cocaine, etc)
- Tachycardia, hypertension, agitation, dilated pupils, seizures

**Opioids/Opiates** (heroin, morphine, methadone, codeine)
- Drowsy → coma, hypoventilation, miosis (tiny pupils)

**Sedative** (benzodiazepines / zolpidem / ethanol)
- Drowsy → coma, staggering, slurred speech, hypoventilation

**Cholinesterase inhibitors** (organophosphate insecticides)
- Bradycardia, bronchoconstriction, small pupils, sweating

**Antimuscarinics** (tricyclic antidepressants, deadly nightshade berries)
- Tachycardia, vasodilatation, pyrexia, dilated pupils

Examples of Poisons with Pharmacological Antidotes

- Paracetamol & N-acetyl cysteine
- Methanol & ethanol
- Opiates & naloxone
- Metals & chelating agent
- Cholinesterase poisoning
  (Anti-digoxin antibodies & anti-venom antibodies: mention only)
Hepatotoxicity

Paracetamol

N-acetyl benzoquinone imine

H2N
COCH3

Cytochrome P450
NADPH, O2

Sulphate &
glucuronide
conjugates

Renal
elimination

Glutathione (GSH)

Glutathione: glu-cys-gly

N-acetyl cysteine
cysteine

Renal
elimination

Paracetamol Treatment Nomogram

Daly FS et al., MJA 2008;188:296-301

Concentration above line treat with N-acetyl cysteine
Treatment of methanol poisoning

CH₃-OH
Alcohol dehydrogenase
C₂H₅-OH (0.2%)

Formic Acid

Acidosis (↓pH)
Inhibits mitochondrial respiration

Dialysis
Dialysis

Ethanol competitively inhibits oxidation to formic acid
Dialysis removes methanol

Examples of Poisons with Pharmacological Antidotes

Opiates & naloxone
- Naloxone is a µ-opioid receptor antagonist
- Given intravenously, rapidly displaces opiate/opioids
- Rapid system clearance: intoxication can resume

Metals & chelating agent
- Succimer (2,3, dimercapto succinate) for As, Pb & Hg
  - → water-soluble sulphydryl complexes
  - → renally excreted
Examples of Poisons with Pharmacological Antidotes

**Anticholinesterase poisons:** Acetyl choline esterase inhibitors
- non-organophosphate (eg carbaryl): competitive inhibitors
- organophosphate sequence of reactions to covalently modify active site → irreversible (eg parathion)

![Chemical structure of parathion](image)

**Toxidrome:** Signs of acetyl choline excess
- Muscarinic & nicotinic
- Impaired consciousness, Small pupils
- Constricted airways
- Slow heart rate
- Gut cramping, vomiting & diarrhoea
- Weak, twitching muscles; sweating

**Antidotes:**
- Atropine to block muscarinic receptors
  (organophosphates require other, specific antidote: not discussed here)

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Examples of Poisons with Pharmacological Antidotes

**Antibodies:**
- Specific antibodies raised against the intoxicant
  - Digoxin & anti-digoxin antibodies
  - Venoms & anti-venom antibodies
    - Snakes
      - Species-specific (monovalent) and polyvalent
    - Spiders
      - Latrodectus hasseltii (red-backed spider)
      - Atrax robustus (Sydney funnel-web)
    - Chironex fleckeri (box jellyfish)
Forensic Toxicology

- Poisoning deaths
- Drug effects on victims of crime
- Drug-related criminality (mostly alcohol or methylnamphetamine)
- Drug-related driving (mostly alcohol or methylnamphetamine, motor vehicle homicides)

Determination of percentage of alcohol at material time

71. (1) In any proceeding such as is mentioned in section 70 (1), the percentage of alcohol present in the blood of a person at any time which is or may be material in the proceeding shall be calculated having regard to that time, the time of the person’s last drink containing alcohol taken at or before the time which is or may be material in the proceeding, and the time at which the sample of the person’s breath or blood was provided or taken for analysis, by varying the analysis result referred to in section 68 or section 69 by such amount, if any, necessary to give effect to the presumption that the percentage of alcohol in the blood of a person increases at the rate of 0.016 per centum per hour for a period of 2 hours after his latest drink containing alcohol and, after that period, decreases at the rate of 0.016 per centum per hour.
Alcohol dehydrogenase
CYP1E2

\[
V = V_m \times \frac{[Alc]}{[Alc]+K_m}
\]

Wagner JG J Pharmacokin Biopharmac 1973;1:103-121
**Enzyme Saturation (%)**

- **Zero order**
  - \( \frac{\Delta \text{Alc}}{\Delta t} = -k \)
  - \( \text{Alc}_t = \text{Alc}_0 - kt \)

- **First order**
  - \( \frac{\Delta \text{Alc}}{\Delta t} = -k \text{Alc} \)
  - \( \text{Alc}_t = \text{Alc}_0 e^{-kt} \)

**Graphs**

- **Ethanol (%)** vs. **Time (hr)**
  - 0.295% at 11:10hr
  - 0.123% at 20:35hr

- **Km = 0.015%**
- **Vm = 0.0175%/hr**

**29 YO male pedestrian**
Practical:

Week 1. Clinical Pharmacology
- Do pre-prac quiz on LMS! Formative
- Series of clinical cases to work through in computer lab: responses audited
- Exit quiz, assessed.

Week 2. Human Toxicology
- Do pre-prac quiz on LMS! Formative
- Series of clinical & forensic toxicology cases to work through in computer lab: responses audited
- Exit quiz, assessed.