PKPD Variability
Quantifying Variability
to aid
Dose Individualization

Nick Holford
University of Auckland

Objectives

1) Learn about the sources of variability in clinical pharmacology
2) Appreciate how a target concentration (TC) strategy is essential for rational drug development and clinical use
3) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM)
4) Understand how to make rational choices for dose individualization

Where are we going?
Pharmacokinetics
Pharmacodynamics
Treatment
Rx = Recipe
PK = Pharmacokinetics: What the body does to the drug
PD = Pharmacodynamics: What the drug does to the body
Rx = Treatment: What the prescribed and patient need to know.
Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).

Variability

N. Sambol CDDS/SUMC1997

Target Concentration

Drug Development and Clinical Use

- Effective drug development needs a plan
  - A good plan has a clear objective
  - TC provides a clear objective in all phases of drug development

- TC is the rational basis for dose individualization
  - Choose the target effect to determine the TC
  - Use TC to predict individual dose

The 1992 view was based on using PKPD for drug development but did not explicitly include how to use medicines in patients.

The target concentration approach links PKPD to prediction of the right dose for a patient.

If Emax and Cs0 and Target Effect are not known then the Target Conc may be estimated from:

Typical Average Daily Dose

Target Conc = \frac{\text{Typical Average Daily Dose}}{\text{Typical Clearance}}

TDM or TCI?

- **Therapeutic Drug Monitoring**
  - TDM Therapeutic Range
    - Imprecise
      - Sub-optimal at borders of the range
    - Toxic
    - Ineffective

- **Target Concentration Intervention**
  - TCI Single Target
    - Accurate
      - Optimal – do the best you can
How to Find the Target?

Randomized concentration controlled trials are the gold standard

Why does PKPD vary?

- **Systematic (predictable)**
  - Body size
  - Disease state (liver, kidney)
  - Genotype
  - etc...

- **Random (not predictable)**
  - Between Subject Variability
  - Within Subject Variability

Predictable Variability

Size and Maturation

- Allometry Alone explains 67% of CL variability
- Allometry + Maturation explains 80% of CL variability

### Unexplained Clearance Variability

<table>
<thead>
<tr>
<th>Drug</th>
<th>BSVU %</th>
<th>WSVU %</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>53</td>
<td>35</td>
<td>Lunn (1997)</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>12</td>
<td>16</td>
<td>Bouillon (1996)</td>
</tr>
<tr>
<td>Riluzole</td>
<td>51</td>
<td>28</td>
<td>Bruno (1997)</td>
</tr>
<tr>
<td>Felodipine</td>
<td>34</td>
<td>33</td>
<td>Wade (1995)</td>
</tr>
<tr>
<td>Drug A</td>
<td>57</td>
<td>29</td>
<td>Karlsson (1993)</td>
</tr>
<tr>
<td>Drug B</td>
<td>35</td>
<td>19</td>
<td>Karlsson (1993)</td>
</tr>
<tr>
<td>Drug B</td>
<td>33</td>
<td>19</td>
<td>Jonsson (1996)</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>22</td>
<td>15</td>
<td>Karlsson (1998)</td>
</tr>
<tr>
<td>Artemisinin</td>
<td>48</td>
<td>53</td>
<td>Sidhu (1998)</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>41</strong></td>
<td><strong>30</strong></td>
<td></td>
</tr>
</tbody>
</table>

BSVU = Between Subject Variability unexplained by predictable factors such as weight, etc.
WSVU = Within Subject Variability unexplained by predictable factors such as weight, etc.

% expresses an apparent co-efficient of variation.

---

### Safe and Effective Variability

**CLINICAL JUDGMENT**
Suppose medicine use is safe and effective if:
1. Individual $C_{ss}$ is on average at the Target Conc
   - Aim for the optimum target
2. 90% of the time $C_{ss}$ is within 80%-125% of Target Conc
   - ‘therapeutic range’ with optimum target

**STATISTICS**
Assume log-normal distribution for $C_{ss}$
90% of $C_{ss}$ must lie within $\pm 1.64 \times SD$
- Therefore SD must be 0.136

The Safe and Effective Variability (SEV) is 13.6%

---

### Three Ways to Dose

- **Population**
  - Same dose for everyone
    - The dream dosing method!

- **Group (Covariate guided)**
  - Same dose for similar group
    - e.g. same weight, CLcr, genotype

- **Individual**
  - Dose determined by individual response
    - e.g. BP, INR, blood conc

---

$C_{ss}$ = Average steady state concentration
SD = Standard Deviation
SEV = Safe and Effect Variability around target concentration
Identifying Variability

- PPV_{total} = Population Parameter Variability total of predictable and unexplained sources
- PPV_{U} = Population Parameter Variability that is unexplained
- BSV_{P} = Between Subject Variability that is predictable
- BSV_{U} = Between Subject Variability that is unpredictable
- WSV_{U} = Within Subject Variability that is unpredictable
- SEV = Safe and Effect Variability around target concentration

Dosing Individualization Method Depends on SEV

Suppose PPV_{total} = 0.7, BSV_{U} = 0.4, WSV_{U} = 0.3

PPV_{U} = \sqrt{BSV_{U}^2 + WSV_{U}^2} = 0.5

BSV_{P} = \sqrt{PPV_{total}^2 - BSV_{U}^2} = 0.57

<table>
<thead>
<tr>
<th>SEV</th>
<th>Method Criteria</th>
<th>Example</th>
<th>Dosing Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>SEV &gt; PPV_{total}</td>
<td>0.9 &gt; 0.7</td>
<td>Population dosing</td>
</tr>
<tr>
<td>0.55</td>
<td>PPV_{total} &gt; SEV, SEV &gt; PPV_{U}</td>
<td>0.7 &gt; 0.55, 0.55 &gt; 0.5</td>
<td>Group dosing (WT, CLcr, etc) (BSV_{U}, 0)</td>
</tr>
<tr>
<td>0.35</td>
<td>PPV_{U} &gt; SEV, SEV &gt; WSV_{U}</td>
<td>0.35 &gt; 0.35, 0.35 &gt; 0.3</td>
<td>Individual response dosing (TCI) (BSV_{U}, 0)</td>
</tr>
</tbody>
</table>

Note: If SEV < WSV_{U}, then medicine cannot be used safely

Safe and Effective Variability (SEV) Aminoglycosides

- Suggested Therapeutic Success Criterion
  - 90% of Concsw within 80%-125% of Target Csa
  - SEV is 0.136 (log normal SD)

- Unpredictable PPV_{U} is 0.33 and is > SEV
  - Covariate (WT, CLcr) prediction alone will be inadequate

- Unpredictable WSV_{U} is 0.13 and is < SEV (just!)
  - TCI can achieve safe and effective target

Which Way to Aim?

- **Phase 2 Drug Development**
  - PK and PKPD relationships (Target Effect $\rightarrow$ Target Conc)
  - Predictable and Unpredictable variability (PPV$_T$)
  - Between (BSV$_U$) and within subject (WSV$_U$)

- **Phase 3 Drug Development**
  - Safe and effective variability (SEV)
  - The BIG difficulty is deciding on SEV!

- **Clinical Use of Medicines**
  - Use quantitative criteria to decide on dosing method
    - Covariate Dosing if PPV$_T$ > SEV > PPV$_U$
    - TCI Dosing if PPV$_U$ > SEV > WSV$_U$

---

The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect.

Why TCI?

- How can a target concentration of 10 mg/L be achieved and maintained?
Which Drugs for TCI?

1. Effect is hard to measure (drug is working when the response is not observable)
   - Anti-arrhythmics e.g. lignocaine
   - Anti-convulsants e.g. phenytoin
   - Anti-coagulants e.g. warfarin

2. Big unpredictable variability (using weight, renal function, etc) and small within subject variability
   - Too much variability means either inadequate beneficial effect or too much adverse effect
   - Observing patient response can predict future dose needs

The first reason for using TCI uses a response, such as BP, as a substitute for being able to measure the clinical disease state that is being treated. When the medicine is working well or it is not working at all the clinical disease state may appear to be the same. It is assumed that trying to reach a typical response that is usually associated with benefit is better than giving everyone the same dose.

The second reason for using TCI is when group based dosing (e.g. using weight) is not enough to reduce the between subject variability so that the medicine can be used safely and effectively. TCI can only work however if the within subject variability (that cannot be influenced by TCI) is small enough so that dose individualization is really predictive for future use of the medicine in the same patient.

How?

Target Concentration Strategy

1. Choose Target Concentration
2. Determine V and CL using WT etc.
3. Calculate LD and MDR
4. Measure Response (e.g. INR)
   - Revise Target Conc
5. Measure Concs
   - Revise V and CL
6. Goto Step 3

The target concentration strategy is an algorithm for reaching the best individual dose. It starts with choosing a target concentration based on pharmacodynamic studies. A group value for volume (V) and clearance (CL) can be determined before the medicine is given. These PK parameters are then used to calculate the initial loading dose (LD) and maintenance dose rate (MDR). A response is measured reflecting how the individual is different from the group of patients who are otherwise similar in weight, genotype, etc. If the response is a measure of drug effect e.g. INR, then it can be used to revise the target conc. If the response is a concentration then it can be used to revise V and CL. Most commonly the focus will be on CL so that a new individualized maintenance dose rate can be calculated.

Target Concentrations

Target Concentrations and Pharmacokinetic Parameters for Selected Medicines (70 kg standard individual). C<sub>ss</sub> is the average steady state concentration.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Conc</th>
<th>Clearance</th>
<th>Volume of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Peak 20 mg/L* C&lt;sub&gt;ss&lt;/sub&gt; 3 mg/L</td>
<td>6 L/h</td>
<td>18 L</td>
</tr>
<tr>
<td>Lincosporin**</td>
<td>150 ng/mL</td>
<td>17 L/h</td>
<td>245 L</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10 mg/L</td>
<td>V&lt;sub&gt;max&lt;/sub&gt;=415 mg/d, Km= 4mg/L</td>
<td>45 L</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2 ng/mL</td>
<td>9 L/h</td>
<td>500 L</td>
</tr>
<tr>
<td>Theophylline</td>
<td>10 mg/L</td>
<td>3 L/h</td>
<td>35 L</td>
</tr>
</tbody>
</table>

* 24 hour dosing ** whole blood

Target concentrations and PK parameters are known for most medicines which are helped by TCI.
Target Effects

Target Effects and Pharmacodynamic Parameters for Selected Medicines. 
Emax is the maximum effect due to the drug, EC50 is the concentration producing 50% of Emax. PEFR is peak expiratory flow rate.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Effect</th>
<th>Emax</th>
<th>EC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>&quot;cure&quot;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>&quot;prevention of rejection&quot;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>&quot;prevention of seizures&quot;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Digoxin</td>
<td>&quot;control of atrial fibrillation&quot;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Theophylline</td>
<td>&quot;normal PEFR&quot;</td>
<td>344 L/min</td>
<td>11 mg/L</td>
</tr>
<tr>
<td>Warfarin</td>
<td>INR 2-3</td>
<td>100%</td>
<td>1.5 mg/L</td>
</tr>
</tbody>
</table>

- Inhibition of prothrombin complex synthesis

The pharmacodynamic parameters for medicines that use TCI are typically not well known. This is a reflection of the difficulty of measuring a clinical response that can be related to concentration.


---

**Determine Group V and CL**

- **Volume of Distribution**
  - size $V = V_{pop} \times \frac{WT}{WT_{std}}$
  - body composition
- **Clearance**
  - size $CL = Cl_{pop} \times \left( \frac{WT}{WT_{std}} \right)^{3/4}$
  - renal function
  - hepatic function
  - concomitant drugs

---

**Calculate LD and MDR**

e.g. gentamicin

- **LD**
  \[ LD = TC \times V \]
  \[ = 20 \, mg/L \times 20 \, L = 400 \, mg \]

- **MDR**
  \[ MDR = TC \times CL \]
  \[ = 3 \, mg/L \times 6 \, L/h = 18 \, mg/h \]
A rational approach to measuring drug concentrations is based on using the measurement to predict pharmacokinetic parameters – most commonly clearance. The least informative time to measure concentrations is just before the next dose (the ‘trough’ concentration) unless this is paired with another ‘peak’ concentration. This is because clearance determines the average concentration. So measuring a concentration in the middle of the dosing interval will be closer to the average and therefore more useful for predicting clearance.

Gentamicin concentrations vary widely in a dosing interval so two concentrations are needed to reliably estimate clearance.

A concentration in the middle of the dosing interval (Ctmid) will be closer to the average steady state concentration (Css) than either a peak or trough concentration. Clearance is easily calculated from CL=DoseRate/Css which can be approximated by CL=DoseRate/Ctmid.
Gentamicin TDS

Gentamicin OD

Gentamicin concentrations with once a day dosing vary considerably. The trough concentration at 24 h is often unmeasurable because it is below the limit of quantitation. Concentrations are best measured 1 h and 8 h after the dose.

References
Holford NHG, Tett S. TDS. Safe and effective variability - A criterion for ideal individualization. Ther Drug Monit 2012;34:S66-70.