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 or Jupiter King of Gods

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).
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 C50 and Target Effect are not known then the Target Conc may be estimated from:

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

Ideal dose prediction requires individual estimates of Emax, C50, V and CL.

**TDM or TCI?**

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

- **Target Concentration Intervention**
  - TCI Single Target
    - Ideal
    - Accurate
    - Optimal – do the best you can
Why TDM Cannot Work

➢ TDM proposes a range of concentrations to judge if an individual is getting the right dose

➢ It is not reasonable to prescribe a range of doses in order to match the range of concentrations

➢ Therefore the therapeutic window cannot be used to get the right dose

➢ There is only one dose that can achieve the target concentration that will produce the target effect

TCI vs TDM - Tacrolimus

➢ TDM
  ➢ Use of TDM had no effect in reducing renal transplant rejection
    – Thervet (2010): Fixed dose vs Genotype dosing (increased fraction within therapeutic window)
    – Anutarakulchai (2019): Fixed dose vs Genotype dosing (increased fraction within therapeutic window, more delayed graft function)

TCI vs TDM - Vancomycin

➢ Three studies compared TCI with historical TDM

➢ All showed TCI achieved more exposure in the therapeutic window than TDM

➢ All showed reduced nephrotoxicity with TCI
TCI vs TDM - Mycophenolate

➢ TCI
  - Use of TCI reduced renal transplant rejection
    - Hale 1998 (Phase 3): Randomized Concentration Controlled Trial. 3 Target AUCs.
    - Le Meur 2008 (APOMYGRE): Fixed Dose vs Target AUC

➢ TDM
  - Use of TDM had no effect in reducing renal transplant rejection
    - van Gelder 2008 (FDCC): Fixed dose vs Therapeutic Window AUC
    - Gaston 2009 (OPTICEPT): Fixed dose vs Therapeutic Window Trough

TCI = goal was to reach target in every patient. Clinicians were given dosing advice using Bayesian estimation.

TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were not given dosing advice.

---

How to Find the Target?


Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
A Randomized Concentration-Controlled Trial

Nicholas Hoford1, Peter Black1, Ron Couch1, Julia Kennedy3 and Robin Briand1
1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand
2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand
3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand

➢ 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

- Toddlers under-predicted
- Toddlers predicted OK
- Neonates over-predicted
- Neonates predicted OK

---

**Unexplained Clearance Variability**

<table>
<thead>
<tr>
<th>Drug</th>
<th>BSV₀ (%)</th>
<th>WSV₀ (%)</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>

**BSV₀**=Between Subject Variability unexplained by predictable factors such as weight, etc.

**WSV₀**=Within Subject Variability unexplained by predictable factors such as weight, etc.

% expresses an apparent coefficient of variation
### Safe and Effective Variability

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

**STATISTICS**
Assume log-normal distribution for \( \text{Css} \)
90% of \( \text{Css} \) must lie within \( 1.64 \times \text{SD} \)
- 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

---

### Identifying Variability

- \( \text{PPV}_{\text{total}} \) = Population Parameter Variability total of predictable and unexplained sources
- \( \text{PPV}_u \) = Population Parameter Variability that is unexplained
- \( \text{BSV}_p \) = Between Subject Variability that is predictable
- \( \text{BSV}_u \) = Between Subject Variability that is unpredictable
- \( \text{WSV}_u \) = Within Subject Variability that is unpredictable
- \( \text{SEV} \) = Safe and Effect Variability around target concentration
Dosing Individualization Method
Depends on SEV
Note: If SEV<WSVu then medicine cannot be used safely

Suppose PPV_total=0.7, BSV_u=0.4, WSV_u=0.3

\[ PPV_U = \sqrt{BSV_u^2 + WSV_u^2} = 0.5 \]

\[ BSV_U = \sqrt{PPV_{total}^2 - BSV_u^2} = 0.57 \]

<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</td>
<td>0.7&gt;0.55</td>
<td>Group dosing (WT, Clcr, etc) (BSV_U &lt;0)</td>
</tr>
<tr>
<td>0.35</td>
<td>PPV_U &gt; SEV</td>
<td>0.5&gt;0.35</td>
<td>Individual response dosing (TCI) (BSV_U &lt;0)</td>
</tr>
</tbody>
</table>

| Covariate (WT, Clcr, etc) (BSV_U <0) |

Note: If SEV<WSVu then medicine cannot be used safely.

Safe and Effective Variability (SEV)
Aminoglycosides

\[ PPV_U, BSV_U, WSV_U \]

\begin{align*}
33 & 0.30 \\
13 & 0.30 \\
\end{align*}

➢ Suggested Therapeutic Success Criterion

\[ 90\% \text{ of Cons Within } 80\%-125\% \text{ of Target Cons} \]

* 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 → Target Conc)
- Predictable and Unpredictable variability (PPV_U)
- 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_U>SEV>PPV_U
  - TCI Dosing if PPV_U>SEV>WSV_U


Matthews I, Kirkpatrick C, Holford NHG. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68
The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect.

Why TCI?


Theophylline: Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
A Randomised Concentration-Controlled Trial

Nicholas Holford1, Peter Black2, Ron Couch3, Julia Kennedy3 and Robin Brune1
1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand
2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand
3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand

➢ 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 Concentrations 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 or 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). Css 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*</td>
<td>6 L/h</td>
<td>18 L</td>
</tr>
<tr>
<td></td>
<td>Cess 3 mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclosporine**</td>
<td>150 ng/mL</td>
<td>17 L/h</td>
<td>245 L</td>
</tr>
<tr>
<td>Phenyltoin</td>
<td>10 mg/L</td>
<td>Vmax=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 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>‘cure’</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>‘prevention of rejection’</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Phenyltoin</td>
<td>‘prevention of seizures’</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Digoxin</td>
<td>‘control of atrial fibrillation’</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Theophylline</td>
<td>‘normal PEFR’</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>

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 \( V = V_{\text{pop}} \times \frac{\text{WT}}{\text{WT}_{\text{std}}} \)
  » body composition

➢ Clearance
  » size \( CL = C_{\text{I_pop}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{std}}}\right)^{3/4} \)
  » renal function
  » hepatic function
  » concomitant drugs

Calculate LD and MDR e.g. gentamicin

➢ LD = \( TC \times V \)
  = 20 mg/L \( \times \) 20 L = 400 mg

➢ MDR = \( TC \times CL \)
  = 3 mg/L \( \times \) 6 L/h = 18 mg/h

When to Measure Concs?

Goal is to estimate PK e.g. CL

➢ Number of Samples
  » Most medicines 1
  » Gentamicin 2

➢ Timing of Sample
  » Most medicines Middle of dosing interval
  » Gentamicin “peak” and “trough”

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.
When to Measure Concs?

Goal is to estimate PK e.g. CL

- Number of Samples
  - Most medicines: 1
  - Gentamicin: 2

- Timing of Sample
  - Most medicines: Middle of dosing interval
  - Gentamicin: “peak” and “trough”

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 

\[ CL = \frac{Dose Rate}{Css} \]

which can be approximated by

\[ CL = \frac{Dose Rate}{Ctmid} \]
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 1h and 8 h after the dose.