TDM is Dead!
Long Live TCI!

Dose Individualization using Monitoring of Patient Response

Nick Holford
University of Auckland

Objectives

1) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM)
2) Appreciate how a target concentration (TC) strategy is essential for rational clinical use of medicines
3) Understand when and why individual patient monitoring can be used for dose individualization

TDM or TCI?

➢ Therapeutic Drug Monitoring
  » TDM Therapeutic Range
    😞 Sub-optimal at borders of the range
  » TDM Therapeutic Range

➢ Target Concentration Intervention
  » TCI Single Target
    😊 Accurate
    ➤ Optimal – do the best you can

TDM = Therapeutic Drug Monitoring
TCI = Target Concentration Intervention

Therapeutic drug monitoring (TDM) is a traditional concept associated with empirical ‘seat of the pants’ dose adjustment determined by a measurement being outside a ‘therapeutic range’. The therapeutic range is hard to identify and is often mistakenly justified because it seems to be similar to the normal reference range for endogenous substances. A concentration at the bottom of the range has a very different meaning (close to being ineffective) from one at the top (close to being toxic) but TDM practitioners usually ignore this and are happy to do nothing as long as the concentration is ‘within range’. TDM is typically limited to measuring a response such as concentration without any clear understanding that the response needs to be used to predict the required dose and to then to administer that dose.

Target concentration intervention (TCI) is a science based method that uses pharmacokinetic and pharmacodynamic principles to identify how patients are different in terms of parameters such as...
CL, V, Emax and C50 and give the dose needed to reach the target. The first component of TCI is to use the individual parameters to predict the dose required to achieve the target as explained above. The second component of TCI is administer the predicted dose in order to achieve the therapeutic target. It has been shown to improve clinical outcome as well as being a cost-effective use of health resources.


Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.

The Evidence - Mycophenolate

- **TCI**
  - Use of TCI linked to reduced renal transplant rejection
    - Hale 1998 (Phase 3): Randomized Concentration Controlled Trial. 3 Target AUCs.
    - Le Meur 2008 (APOMYGYRE): 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 Range AUC
    - Gaston 2009 (OPTICEPT): Fixed dose vs Therapeutic Range 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.


The Evidence - Tacrolimus

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

TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were given dosing advice.

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 range 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

Target Concentration in Clinical Use of Medicines

\[
\text{Target Conc} = \frac{\text{Target Effect} \times C50}{(\text{Emax-Target Effect})}
\]

<table>
<thead>
<tr>
<th>Target Conc</th>
<th>Dose Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Peak</td>
<td>Loading Dose = Target Conc x Volume of Distribution</td>
</tr>
<tr>
<td>Average Steady State</td>
<td>Maintenance Dose Rate = Target Conc x Clearance</td>
</tr>
</tbody>
</table>

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

The target concentration approach links pharmacokinetics (PK) with pharmacodynamics (PD) to predict the right dose for a patient.

How can the target concentration be calculated if there is no pharmacodynamic model available? Suppose the target effect for morphine is to reduce post-operative pain to an acceptably mild degree without unacceptable adverse effects. A commonly recommended dose of morphine sulfate is 5 mg repeated every 4 h according to response (New Zealand Formulary 2019). Because morphine sulfate is only 75% morphine this corresponds to a morphine dose of 3.76 mg/4h or 0.94 mg/h. The plasma clearance is about 86 L/h/70 kg (Holford, Ma et al. 2012) so the steady state target concentration is 0.94/86 = 0.011 mg/L. The steady state volume of distribution of morphine is about 350 L/70 kg so the intravenous loading dose is 350 L x 0.011 mg/L which is about 3.8 mg morphine or 5.1 mg morphine sulfate. This loading
dose is consistent with the usual starting dose of 5 mg morphine sulfate. This shows how the target concentration can be worked out based on doses that have already been worked out by trial and error.


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.


**Target Concentrations**

**Target Concentrations and Pharmacokinetic Parameters for Selected Medicines (70 kg standard individual).** Cass 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>Tacrolimus**</td>
<td>10 mcg/L</td>
<td>20 L/h</td>
<td>100 L</td>
</tr>
<tr>
<td>Phenytoin</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>1 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 standardized to haematocrit 45%

---

**How to Find the Target?**


Theophylline Target Concentration in Severe Airways Obstruction - 10 or 20 mg/L?

A Randomised Concentration-Controlled Trial

Nicholas Holford\(^1\), Peter Black\(^1\), Ron Couch\(^2\), Julia Ekeady\(^3\) and Robin Briand

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

---

For some drugs a so called therapeutic window of concentrations has been established by a similar trial and error approach. This range of concentrations is better thought of as an acceptable range but it does not define the target concentration. With the initial guidance of the acceptable range a clinical trial can compare potential target concentrations. This approach was used find the target concentration for starting treatment with theophylline in patients with severe airways obstruction (Holford, Black et al. 1993). Patients were randomized to targets of 10 and 20 mg/L and clinicians adjusted the dose after measuring concentrations to reach the target. This trial showed 10 mg/L was better than 20 mg/L. It produced a reasonable bronchodilator effect without serious adverse effects. The results were subsequently analyse to develop a pharmacodynamic model for theophylline (Holford, Hashimoto et al. 1993) (Holford 2017)


How to Dose?
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. Conc [,INR])
5. Interpret Response
   Revise V and CL [,C50]
6. Goto Step 3

Determine Group V and CL (predictable variability)

- **Volume of Distribution**
  - size
    \[ V = V_{pop} \times \frac{WT}{WT_{std}} \]
  - body composition

- **Clearance**
  - size
    \[ CL = C_{pop} \times \left( \frac{WT}{WT_{pop}} \right)^{3/4} \]
  - renal function
  - hepatic function
  - concomitant drugs

The target concentration strategy is an algorithm for reaching the best individual dose. It starts with choosing a target concentration (Sheiner and Tozer 1978). A group value for volume (V) and or clearance (CL) is 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, renal function, 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.

Calculate LD and MDR  
**e.g. Gentamicin**

- **LD** = TC \( \times \) V  
  \[
  = 20 \text{ mg/L} \times 20 \text{ L} = 400 \text{ mg}
  \]

- **MDR** = TC \( \times \) CL  
  \[
  = 3 \text{ mg/L} \times 6 \text{ L/h} = 18 \text{ mg/h}
  \]
  \[
  = 400 \text{ mg/day}
  \]

**When to Measure Concs?**

**Goal is to estimate PK e.g. CL**

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

- **Timing of Sample** - As soon as possible
  - 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. The sooner the sample is taken the sooner concentrations can be used to improve dosing.
A concentration in the middle of the dosing interval (C_{Tmid}) will be closer to the average steady state concentration (C_{ss}) than either a peak or trough concentration.

Clearance is easily calculated from \( CL = \frac{DoseRate}{C_{ss}} \) which can be approximated by \( CL = \frac{DoseRate}{C_{Tmid}} \).

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. In this example a dose of 240 mg was given every 24 hours.

In this example a dose of 240 mg was given every 24 hours. 

\[ V = 0.85 \times \frac{Dose}{C_1} \approx 0.85 \times \frac{240 \text{ mg}}{13 \text{ mg/L}} = 15.7 \text{ L} \]

\[ K = \frac{\ln(C_1/C_2)}{(T_2 - T_1)} = \frac{\ln(13/8)}{(8-1)} = 0.236 \text{ h}^{-1} \]

\[ T_{half} = \frac{\ln(2)}{K} = \frac{\ln(2)}{0.236} = 2.94 \text{ h} \]

\[ CL = V \times K = 15.7 \times 0.236 = 3.7 \text{ L/h} \]
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
¾ Allometry Alone explains 67% of CL variability
¾ Allometry + Maturation explains 80% of CL variability

Propofol is a commonly used intravenous anaesthetic whose dose is largely predictable from weight and age (Figure 1). This figure shows observed clearance values (red) over a wide range of weight and ages. Predictions of clearance based only in weight (allometry) or weight combined with age (maturation) show that up to 80% of variation in clearance is predictable and this can be used to work out the infusion rate of propofol. The plasma clearance of propofol in a 70 kg adult is about 2 L/min or 120 L/h and the target concentration is 5 mg/L so the required infusion rate is 600 mg/h.

Holford NHG. Target concentration intervention - can we hit the targets? 6th International Symposium on Measurement and Kinetics of In Vivo Drug Effects; Noordwijkheirt. LACDR; 2010.

Differences Remain Even After Accounting for Obvious Features

It shows the frequency distribution of clearance (expressed per kg body weight) for a medicine eliminated largely by metabolism with the distribution of clearance in specific sub-populations. Despite the use of weight, sex, age, disease, concomitant medications there remains a substantial variability of clearance within each sub-population. This remaining variability is what TCI can reduce. The limiting variability for the benefit of TCI is within subject variability.

Theophylline is metabolized by CYP1A2. This enzyme is induced by polycyclic hydrocarbons in cigarette smoke. Enzyme induction reduces variability because there is a maximum biological limit on the extent of enzyme induction.

Note that the naive per kg method of scaling leads to an apparent higher clearance in children but in fact the clearance in children is the same as adults when scaled based on allometric theory (Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.)

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 WSVU=Within Subject
Safe and Effective Variability

➢ CLINICAL JUDGMENT
Suppose medicine use is safe and effective if:
1. Individual Css is on average at the Target Conc
   - Aim for the optimum target
2. 90% of the timeCss is within 80%-125% of Target Conc
   - 'acceptable range' with optimum target

➢ STATISTICS
Assume log-normal distribution for Css
90% of Css must lie within $1.64 \times SD$
- Therefore SD must be 0.136

The Safe and Effective Variability (SEV) is 13.6%

The Acceptable Range

➢ Target Concentration Intervention proposes an acceptable range.
➢ This is similar to the therapeutic range but is applied at the level of the population not the individual.
➢ The acceptable range is used to decide on a dosing strategy for the population in order to determine the acceptable dose individualization method.

There are 3 ways to think about choosing the dose.
The population dosing method uses the same dose for everyone. It is the most commonly used method but usually just for convenience. This means that some patients are either under-dosed or over-dosed.
The group dosing method uses patient factors (also known as covariates) to predict the dose suitable for a group of patients with similar factors. Dosing in children is nearly always based on weight or age. The use of weight or renal function to adjust the dose is recommended for some medicines but probably not used as often as it should be.
Individual dosing based on patient response is widely used when the response is easily measured. For example anti-hypertensive doses are usually adjusted based on the blood pressure response. The use of other response markers such as the international normalized ratio (INR) response to warfarin or the concentration of an
antibiotic such as gentamicin are also examples.

\[ \text{CLcr} = \text{Creatinine clearance}, \ BP = \text{Blood Pressure}, \ \text{INR} = \text{International Normalized Ratio} \]

Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.

### Dosing Individualization Method Depends on Safe and Effective Variability (SEV)

Suppose \( PPV_{\text{total}} = 0.7, \ BSV_U = 0.4, \ WSV_U = 0.3 \)

\[
PPV_U = \sqrt{BSV_U^2 + WSV_U^2} = 0.5 \\
BSV_U = \sqrt{PPV_{\text{total}}^2 - BSV_U^2} = 0.57
\]

<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_{\text{total}} )</td>
<td>( 0.9 &gt; 0.7 )</td>
<td>Population dosing</td>
</tr>
<tr>
<td>0.55</td>
<td>( PPV_{\text{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 \arepsilon 0) )</td>
</tr>
<tr>
<td>0.35</td>
<td>( PPV_U &gt; SEV ) ( SEV &gt; WSV_U )</td>
<td>( 0.5 &gt; 0.35 ) ( 0.35 &gt; 0.3 )</td>
<td>Individual response dosing ( \text{(TCI)} ) ( (BSV_U \arepsilon 0) )</td>
</tr>
</tbody>
</table>

Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68

### Safe and Effective Variability (SEV) Aminoglycosides

<table>
<thead>
<tr>
<th>( PPV_U )</th>
<th>( BSV_U )</th>
<th>( WSV_U )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.33</td>
<td>0.30</td>
<td>0.13</td>
</tr>
</tbody>
</table>

➢ Suggested Therapeutic Success Criterion

- 90% of Conc within 80%-125% of Target C\( \text{ss} \)
- \( \text{SEV is 0.136 (log normal SD)} \)

➢ 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

Know Your Target
Be Courageous

➢ Target for drug development is to learn
  • the concentration effect relationship
  • safe and effective variability

➢ Target for clinical practice is to confirm
  • Target effect and target concentration
  • Best method for achieving the target effect for the patient

➢ PKPD provides the tools to achieve the targets
  • time to move away from traditional empirical approaches.
  • drug developers and clinicians must have courage to change

➢ Take Aim and Hit the Target!