Target Concentration Intervention

Dose Individualization using Monitoring of Patient Response

Nick Holford
University of Auckland

Objectives

1) Appreciate how a target concentration (TC) strategy is essential for rational clinical use of medicines

2) Understand when and why individual patient monitoring can be used for dose individualization

3) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM)

Target Concentration in Clinical Use of Medicines

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...
How to Find the Target?


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 Briant2

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

---

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.


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)


**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

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

---

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; Noordwijkerhout. 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 naïve 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.)

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.

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

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

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

2. Big unpredictable variability (after 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

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 Cons
   - Revise V and CL
6. Goto Step 3

The first reason for using TCI is when the effect of treatment on the desired outcome cannot be easily measured. Cardiac anti-arrhythmic drugs and brain anti-arrhythmic drugs (anti-convulsants) may be having a useful effect but often arrhythmias (heart or brain) occur only intermittently so it hard by direct observation to know if they are effective. TCI can be used here to ensure that drug concentration, a surrogate for anti-arrhythmic effect, is at a target which is known to be effective in most people.

The second reason for using TCI is when group based dosing (e.g. using weight) is not enough to reduce between subject variability enough. Group based dosing removes the predictable component of between subject variability but the remaining unpredictable component may still be too large for the medicine to be used safely and effectively. This is where the use of individual patient response can further reduce variability and improve the probability of patients being within a acceptable range around the target concentration. Eventually a limit is reached attributable to within subject variability that cannot be influenced by TCI.

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.

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>Css 3 mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus**</td>
<td>7 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

Target Effects

Target Effects and Pharmacodynamic Parameters for Selected Medicines. Emax is the maximum effect due to the drug, C50 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>C50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>&quot;cure&quot;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Tacrolimus</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 (predictable variability)

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

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

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 ($C_{t_{mid}}$) 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 $CL = \frac{DoseRate}{C_{t_{mid}}}$.

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

$V$ can be approximated from the first conc ($C_1 \approx 13 \text{ mg/L}$) assuming about 15% of the dose is eliminated in 1 hour. $V = 0.85 \times \frac{\text{Dose}}{C_1} \approx 0.85 \times \frac{240 \text{ mg}}{13 \text{ mg/L}} = 15.7 \text{ L}$

Half-life can be estimated from $C_1$ at time $T_1$ (1 h) and the second conc ($C_2 \approx 2.5 \text{ mg/L}$) at time $T_2$ (8 h):

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

$T_{\text{half}} = \frac{\ln(2)}{K} = 2.94 \text{ h}$

$CL$ can then be calculated:

$CL = V \times K = 3.7 \text{ L/h}$

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.

Assessment Short Answer
Question Examples

1. Define what is meant by a target concentration.

2. Give an example of a medicine and the response used for individual patient monitoring and dose individualization.

3. Describe two components of target concentration intervention which distinguish it from therapeutic drug monitoring.