Target Concentration
Intervention

Dose Individualization using Monitoring of Patient Response

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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

Target Concentration = Target Effect x C50 / (Emax - Target Effect)

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
contentration can be worked out
based on doses that have already
been worked out by trial and
error.

Holford NH, Ma SC, Anderson BJ.
Prediction of morphine dose in
humans. Paediatr Anaesth.
New Zealand Formulary.
Morphine monograph
https://nzf.org.nz/nzf_2515
2019

How to Find the Target?

➢ 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). Hale
et al (1998) and Shaffer et al
(2002) are examples of TCI trials
used to determine the exposure-
response relationship.

Holford, N., P. Black, R. Couch, J.
"Theophylline target concentration
in severe airways obstruction - 10
or 20 mg/L? A randomised
concentration-controlled trial." Clin
Holford, N., Y. Hashimoto and L.
B. Sheiner (1993). "Time and
theophylline concentration help
explain the recovery of peak flow
following acute airways
obstruction. Population analysis of
a randomised concentration
controlled trial." Clin
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.

Differences Remain Even After Accounting for Obvious Features


Figure originally drawn by Dr N.Sambol CDDS/SUMC1997

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.)
Three Ways to Dose

- **Population**
  - Same dose for everyone
  - The dream dosing method! (often used in adults)

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

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

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.

CLcr = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio


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

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
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.


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**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

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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.
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>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

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

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

\[\text{WT}=\text{patient weight}\]
\[\text{WT}_{\text{std}}=\text{standard weight e.g. 70 kg}\]
\[V_{\text{pop}}, CL_{\text{pop}}=\text{population volume and clearance in a standard subject e.g. 70 kg.}\]

Calculate LD and MDR e.g. Gentamicin

➢ LD = TC x V
  = 20 mg/L x 20 L = 400 mg

➢ MDR = TC x CL
  = 3 mg/L x 6 L/h = 18 mg/h
  = 400 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=DoseRate/C_{ss} which can be approximated by CL=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. 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 \text{Dose}/\text{C}_1 \text{ e.g. } 0.85 \times 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=\ln(C_1/C_2)/(T_2-T_1)=\ln(13/8)/(8-1)=0.236 \text{ h}^{-1}

Thalf=\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 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.
## Principles of TDM and TCI

<table>
<thead>
<tr>
<th>Principle</th>
<th>TDM</th>
<th>TCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has a single target</td>
<td>TDM does not have a target. It provides a range (“therapeutic window”) that does not directly lead to a suitable dose.</td>
<td>TCI has a single target. The target can be used easily to calculate a suitable dose.</td>
</tr>
<tr>
<td>Uses PKPD principles</td>
<td>TDM only provides a measured concentration.</td>
<td>TCI uses PKPD principles to estimate individual parameters which can then be used to calculate a suitable dose.</td>
</tr>
<tr>
<td>Provides guidance to the clinician for the next dose</td>
<td>TDM does not provide guidance except through a “therapeutic” window which cannot be used to calculate a suitable dose. Dose adjustments are often empirical, rather than based on quantitative pharmacological rationale.</td>
<td>TCI uses the target and individual parameters such as clearance to recommend to the clinician a suitable dose.</td>
</tr>
</tbody>
</table>

## 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. List the principles of target concentration intervention which distinguish it from therapeutic drug monitoring.