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).

Based on the law of mass action principle the binding of a drug to a receptor should follow a hyperbolic curve (as shown here). If it is assumed that the effect is directly proportional to the binding then the C50 will be the same as the Kd (the equilibrium binding constant). Notice that Emax can never be directly observed. It is the asymptotic effect of the drug at infinite concentration. Even 10 times the C50 only reaches 90% of Emax.
Elimination Clearance

CL = Rate Out/Concentration

The bathtub provides a physical model to explain how clearance determines drug elimination. This bathtub has fixed rate of water flowing in from the tap (rate in = 4 drops/unit time). Water is lost from the bathtub at the same rate (rate out = 4 drops/unit time) which keeps the bath water level constant (steady state). Clearance is determined by the size of the hole in the bathtub.

Volume of Distribution

\[ V = \frac{Amount}{Conc} \]

The bathtub provides a physical model to explain how physical factors can influence the apparent volume. In this example there is no loss of water from the bathtub. By putting a known amount of drug (the dose) into the bathtub and measuring the concentration it is easy to calculate the apparent volume.

Target Concentration in Clinical Use of Medicines

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

\[ \text{Target Conc} = \frac{\text{Target Effect} \times C50}{E_{\max} - \text{Target Effect}} \]

Ideal dose prediction requires individual estimates of E_{\max}, C50, Volume and Clearance.
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.

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In the clinic patients will have exposure within, at the limit of, and outside the acceptable range. They will be distributed within and across the therapeutic window. The therapeutic drug monitoring approach, assumes, that all our patients sit within the flags. This assumption is not correct.

The second fallacy of TDM is what is done with a concentration measurement; what should be the magnitude of the dose change given a measured concentration? What should we do if the measurement is just inside or outside the acceptable range (e.g. 28 or 31 in this example)? Furthermore this approach assumes that there is a range of doses which match the acceptable range of concentrations. The maintenance dose rate is related to the target concentration and clearance. Clearance will time with time, but is constant at a single point in time. The target concentration can only be achieved by a single maintenance dose. It is not possible to have a range of targets (e.g. 28 to 31) as this will require a range of maintenance dose rates.

We can be more accurate and precise if we remove the flags and aim for a specific target. In the target concentration intervention approach, every measurement is used to guide dose adjustment to achieve a target concentration a measure which is correlated with improved outcomes. As described previously, maintenance dose rate is related to the target concentration and clearance. Therefore if we know the clearance for an individual, then the maintenance dose rate is known. Target concentration intervention also provides a method to link target concentration with dose. This means that the clinician is provided a proposed dose that will achieve the target.
**Slide 13**

**TDM or TCI?**

- Therapeutic Drug Monitoring
  - TDM Therapeutic Range
    ☹ Sub-optimal at borders of the range

- Target Concentration Intervention
  - TCI Single Target
    ☺ Accurate
    - Optimal - do the best you can

**Slide 14**

**Busulfan Pharmacodynamics**

![Graph](image)

- **Proposed Range** 0.6 to 0.9 mg/L; **Target Concentration** 0.77 mg/L
- **Corresponds to Target** $AUC_{ssDI}$ of 1125 umol*min q6h dosing


$AUC_{ssDI}$ = Area under the concentration time curve at steady state over the dosing interval

**Slide 15**

**AUC Dose Adjustment from Busulfex label (PDL 2006)**

- **Dose Adjustment Based on Therapeutic Drug Monitoring**
  - For measuring the AUC of busulfan plan 1 dose based on literature average steady state concentration (0.77 mg/L) with a 6 h dosing interval.

The FDA label is complex and detailed. It recommends an AUC using umol/L derived from the target from the literature average steady state concentration (0.77 mg/L) with a 6 h dosing interval. There is no rationale for using mass units (umol/L) but there is a rational argument for using mass units because they are the same units as the dose (mg). This simplifies the calculation of the dose.
Bayesian Dose Adjustment

- Well established methodology for TDM based dose prediction
  - Sheiner 1977
  - Applied to busulfan paediatric BMT (Bleyzac 2001, Salinger 2010)
- Flexible
  - Not affected by sampling times (provided they are accurate)
  - First dose can be loading dose > maintenance dose
- Output
  - Estimate of patient’s clearance (CL) and dose
  - Any dosing interval (e.g. q6h, daily, continuous infusion)

\[
\text{Dose mg q interval h} = 265 \text{ mg q 24 h} = \frac{0.770 \text{ mg/L} \times 14.3 \text{ L/h}}{24 \text{ h}}
\]

AUC vs Bayesian Dose Adjustment

- Simulated concentrations without error
- AUC linear or linear/log trapezoidal
- Bayesian pharmacokinetic model

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.
**The Evidence – Vancomycin**

- Three studies compared TCI with historical TDM
- All showed TCI achieved more exposure in the therapeutic range than TDM
- All showed reduced nephrotoxicity with TCI

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

TDM = goal was to reach target trough within therapeutic range in every patient. Clinicians may have been given dosing advice (varied by study).


**The Evidence – Mycophenolate**

- TCI
  - Use of TCI 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.


Busulfan Target Exposure

AUC vs Event Free Survival

Acceptable Range 78 to 101 mg/L*h over 4 days
Target AUC 90 mg/L*h over 4 days

EFS = event-free survival

Practical Questions

- Number and timing of blood samples for busulfan measurement?

- Should doses be adjusted to achieve
  - Target AUC – ignoring whether initial doses were too or too low?
  - The traditional goal
  or
  - Total treatment period target AUC – adjust subsequent doses to achieve cumulative dose?
  - The pharmacological theory goal


Figure 2: Polynomial Weibull models of the association between busulfan cumulative area under the curve and event-free survival
(A) The polynomial Weibull model of the association between busulfan cumulative AUC and EFS (using uncensored data) is able to reproduce the central tendency, because all raw EFS data of the Δ 5 mg × h/L AUC groups (dots) in the training (blue solid line) and internal validation datasets (blue dashed line) fall within the 95% CI of the model predicted association between busulfan cumulative AUC and EFS. (B) The busulfan cumulative AUC and EFS polynomial Weibull model stratified by malignant (red solid line) and non-malignant (blue dashed line) underlying disease shows that the optimum AUC does not depend on indication. The red shaded rectangles show the historical target, as defined in previous studies.13,15,26,27 The green shaded rectangles show the target defined in the present study. Shaded areas represent 95% CIs. AUC = area under the curve. Css = concentration at steady state.
Conclusion


NextDose target concentration intervention report for a patient after the first dose of busulfan. The trapezoidal AUC and dose predicted from the AUC are shown only to compare with the Bayesian predicted dose which is expected to be more reliable. The Bayesian estimate of clearance is 36.7% higher than expected based on the patients age and size.

The measured busulfan concentrations are shown with population predictions based on the dose, age and size. The yellow line shows the Bayesian predicted concentrations based on the measured concentrations and population prior information.