Presented at AAPS Annual Meeting 15 Nov 2016 Denver Colorado USA in a session entitled “A religious debate between clearance (CL) and rate constant (kel) camps!”

Slide 1

Clearance is My Religion

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Slide 2

Religion

I have been a brown water drinker ever since 1998 during sabbatical in Washington DC

Clearance – the only rational religion

1) Brown water is a fluid input
2) Yellow water is a fluid output
3) Both fluid input and output are important for a happy life
4) Fluid input and outputs may be quantified as flows
5) Clearance is a flow parameter
6) Therefore clearance helps me live a happy life and go with the flow!

Slide 3

Clinical Pharmacology

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).
Clearance
“The Holy Trinity”

Clearance describes the relationship between concentration and the rate of elimination of drug from the body

Elimination = CL × Concentration

Note that elimination (mg/h) and clearance (L/h) are NOT the same thing

The definition of clearance (CL) links drug concentration to the rate of elimination (rate out). Note that elimination and clearance are NOT the same thing.

Because the definition of clearance is linked directly to concentration it is important to know in what fluid the concentration is obtained. Most commonly drug clearance is based on drug concentration in plasma or serum. For all practical purposes there is no difference between plasma and serum concentrations.

Theophylline Target Concentration

Clinical Pharmacokinetics. 23 (6): 493-503, 1993

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

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- How can a target concentration of 10 mg/L be maintained?

Maintenance Dose Rate

- At Steady State:
  
  Elimination Rate = Input Rate

- Therefore

  Elimination = CL × Concentration

  \[ mg/h = L/h \times mg/L \]

  \[ 30 \, mg/h = 3 \, L/h \times 10 \, mg/L \]
Concentration Dependent Clearance

\[ \text{Rout} = \left( \frac{V_{\text{max}}}{K_m + C} \right) \cdot C \]

- Mixed Order
- First Order
- Zero Order

Rout = Rate out

The order of a chemical reaction can be defined in terms of the number of reactive species determining the rate of the reaction (https://en.wikipedia.org/wiki/Order_of_reaction).

Enzymatic reactions are typically saturable and can be described in terms of the maximum rate of elimination (Vmax) and the concentration producing 50% of Vmax (Km).

Most enzymatic drug metabolism (i.e. elimination) is driven primarily by the drug concentration. If concentration is small in relation to Km then the elimination rate will appear to be first-order i.e. linearly dependent only on concentration. If concentrations are large in relation to Km then the elimination rate will appear to be independent of concentration. This is called a zero-order reaction.

Concentrations that are neither small nor large in relation to Km will give rise to a mixed-order reaction. The mixed-order reaction should be considered as the general case for all drugs eliminated by metabolism. The first-order approximation is very common. True zero-order elimination does not occur in reality but may be approximated at very high concentrations.

Applications

- Additional elimination processes
  - Haemodialysis
  - Haemoperfusion
  - Gut adsorption (charcoal)

- Clearance from each process gives a simple quantitative guideline for usefulness in treating poisoning

The benefits of treatments intended to enhance elimination after poisoning can be evaluated by comparing the clearance by the treatment to the expected drug clearance without treatment. Haemodialysis is the same procedure used for patients with renal failure. Haemodialysis clearance is relatively low. For example, haemodialysis clearance of theophylline is 4 L/h. While this is low compared to clearance of other drugs it is similar to the metabolic clearance of theophylline and thus can substantially increase theophylline elimination.

Haemoperfusion involves passing blood through a cartridge designed to adsorb the drug. Haemoperfusion clearance can be double that of haemodialysis (e.g. theophylline haemoperfusion clearance is 9 L/h) but there is wide drug to drug variability (Cutler, R.E., Forland, S.C., Hammond, P.G.S. & Evans, J.R. Extracorporeal Removal of Drugs and Poisons by Hemodialysis and Hemoperfusion. *Annu Rev Pharmacol Toxicol* 27, 169-91 (1987)).

Adsorption of drug in the gut by activated charcoal can enhance elimination by preventing primary absorption and re-absorption from drug passing from the body passively back into gut fluids. Activated charcoal can double theophylline clearance from 3 L/h to 6 L/h.
**Target Concentration in Clinical Use of Medicines**

**Target Conc = Target Effect x C50 / (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

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**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. weight (usually used for children), CLcr, genotype

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

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**How?**

**Target Concentration Strategy**

1. Choose Target Concentration
2. Determine CL using WT etc.
3. Calculate Maintenance Dose Rate
4. Measure Concentration
   Revise CL based on individual concentration
5. Goto Step 3

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

The population dosing method is most commonly used but usually just for convenience. This means that some patients are either under-dosed or over-dosed.

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.

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

Individual dosing based on response is widely used when the response is easily measured. But sometimes it is used e.g. with anti-HIV medicines, when the within subject variability is large and predictable individualization is not really possible.

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

- Clearance
  - size  $CL = Cl_{pop} \times (WT/WT_{std})^{3/4}$
  - renal function
  - hepatic function
  - concomitant drugs
  - ...

Calculate Maintenance Dose Rate e.g. Digoxin

- $MDR = TC \times CL$
  - $1 \text{ mcg/L} \times 6 \text{ L/h}$
  - $6 \text{ mcg/h IV}$
  - $6 \times 24/0.65 \text{ mcg/day Oral}$
  - $221 \text{ mcg/day}$

Prescribe 0.25 mg once a day

When to Measure Concs?

Goal is to estimate Clearance

- Number of Samples
  - Most medicines: One sample
- Timing of Sample
  - As soon as possible
    - Most medicines: Middle of dosing interval

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 (Tmid) 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 $CL = \frac{Dose\ Rate}{CTmid}$.

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**My Rational Religion is Clear(ance)**

- Widely understood
- Science and Biology based
- Directly applicable to clinical decisions
Imagine a patient stabilized on digoxin.
The patient is involved in a car crash and has both legs amputated.
Renal and hepatic function are normal.

- What happens to CL? Nothing
- What happens to V? Smaller
- What happens to half-life? Shorter

Dr. Bigger’s statement about the relation between volume and clearance probably arises from the familiar pharmacokinetic equation:
\[
\text{clearance} = K_d \times V_d
\]
where \(K_d\) is the elimination rate constant, and \(V_d\) the volume of distribution. Although clearance appears on the left side of the equation, it is not the dependent variable; \(K_d\) is the dependent variable, and it is determined by the relative sizes of the independent variables: clearance and \(V_d\). Therefore, a reduction in \(V_d\) can be expected to decrease \(K_d\) and thus decrease the half-life, provided that clearance does not change. But in the case of digoxin and quinidine, clearance is also reduced (to the same degree as \(V_d\)), and therefore the half-life does not change. This misunderstanding of the relation between clearance, volume, and half-life is common and emphasizes the fact that clinical pharmacokinetics must be based on an understanding of underlying physiology and not simply algebra.

Any clearance + volume model can be re-parameterized in terms of rate constants.
- Advantage: Clearance and volume are connected to biology (“PBPK”)
- Advantage: Calculation code is simpler and may be faster using rate constants

Turnover of prothrombin complex activity (PCA) has a half-life of around 14 hours. This explains the delay in warfarin response.
Not all Reparametizations are Equivalent

- Compared CL, V with K, V
- One compartment, first-order input, first-order elimination
- Mixed Effects Model
- Variability of F only identifiable with CL, V