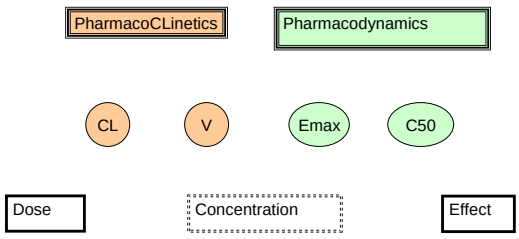
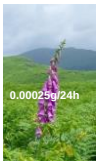
Slide 1	# Clearance is My Religion NicCL Holford Dept Pharmacology & Clinical Pharmacology **University of AucCLand**	Presented at AAPS Annual Meeting 15 Nov 2016 Denver Colorado USA in a session entitled “A religious debate between clearance (CL) and rate constant (kel) camps!”
Slide 2	# Religion I 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).

Slide 4	**Clearance** **"The Holy Trinity"** *Clearance describes the relationship between concentration and the rate of elimination of drug from the body* $Elimination = CL \times Concentration$ **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.
Slide 5	**Theophylline Target Concentration** Clin. Pharmacokinet. 25 (6): 495-505, 1993 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 Kennedy*[3] and *Robin Briant*[1] 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 ● How can a target concentration of 10 mg/L be maintained? 	A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital. It showed that the target concentration is 10 mg/L. Higher concentrations had little extra benefit but substantially more toxicity e.g. nausea and vomiting. If the target concentration is known what dose rate is needed to maintain the concentration at the target?
Slide 6	**Maintenance Dose Rate** ● At Steady State: $Elimination\ Rate = Input\ Rate$ ● Therefore $Elimination = CL \cdot Concentration$ $mg/h = L/h \cdot mg/L$ $30\ mg/h = 3\ L/h \cdot 10\ mg/L$ 	Maintenance dose rate can be predicted if the target concentration and the drug clearance are known. Steady state drug concentrations are maintained when the rate of drug administration (rate in) is equal to the rate of elimination (rate out). Using the definition of clearance we can predict the steady state rate in. Note the units of clearance are typically L/h and concentration is mg/L. Maintenance dose rates are then readily predicted with units of mg/h.

Slide 7

Concentration Dependent Clearance



$$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$

Mixed Order

$$Rout = \left[\frac{V\max}{Km_{+C}}\right] \cdot C$$

$$Rout = CL \cdot C$$

First Order

$$Rout = \left[\frac{V\max}{Km_{+}C}\right] \cdot C$$

$$Rout = V\max$$

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.

Slide 8

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 haemoperfuson 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.

Slide 9

Target Concentration in Clinical Use of Medicines

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

Target Conc	Dose Model
Initial Peak	Loading Dose = **Target Conc** x **Volume of Distribution**
Average Steady State	Maintenance Dose Rate = **Target Conc** x **Clearance**

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.

Slide 10

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

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.

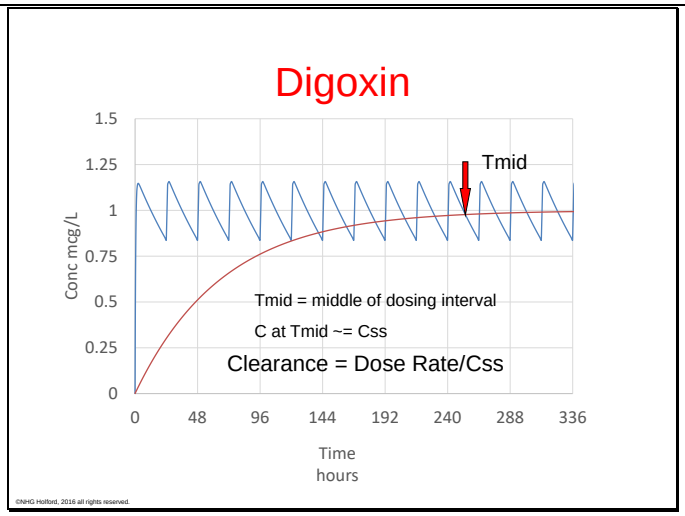
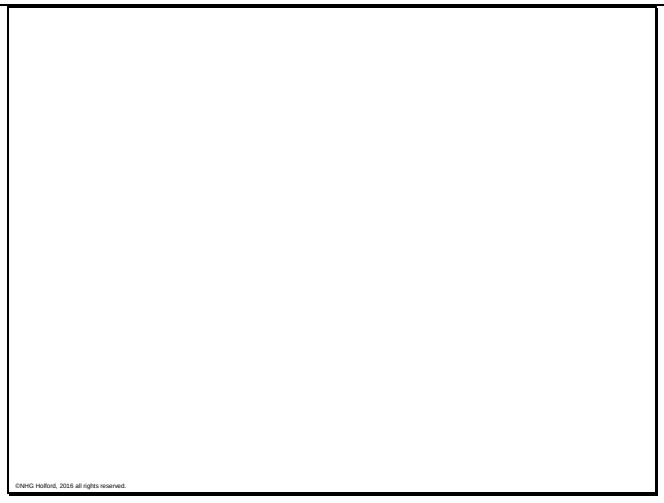
Slide 11

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

The target concentration strategy is an algorithm for reaching the best individual dose. It starts with choosing a target concentration based on pharmacodynamic studies. A group value for volume (V) and or clearance (CL) can be 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, genotype, 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.

Slide 12	**Group Clearance** (predictable variability) ● Clearance » size CL = Cl_{pop} x $(WT/WT_{std})^{3/4}$ » renal function » hepatic function » concomitant drugs » … 	WT=patient weight WTstd=standard weight e.g. 70 kg Vpop, CLpop=population volume and clearance in a standard subject e.g. 70 kg.
Slide 13	**Calculate Maintenance Dose Rate** **e.g. Digoxin** ● MDR = TC x CL = 1 mcg/L x 6 L/h = 6 mcg/h IV = 6*24/0.65 mcg/day Oral = 221 mcg/day Prescribe 0.25 mg once a day 	
Slide 14	**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.

Slide 15		A concentration in the middle of the dosing interval (Ctmid) will be closer to the average steady state concentration (Css) then either a peak or trough concentration. Clearance is easily calculated from CL=DoseRate/Css which can be approximated by CL=DoseRate/CTmid.
Slide 16		
Slide 17		

Slide 18	**CL and V Independence** ● 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 Holford NH. The quinidine-digoxin interaction. N Engl J Med. 1980;302(15):864. 	Dr. Bigger's statement about the relation between volume and clearance probably arises from the familiar pharmacokinetic equation: clearance = Kd X Vd where Kd is the elimination rate constant, and Vd the volume of distribution. Although clearance appears on the left side of the equation, it is not the dependent variable; Kd is the dependent variable, and it is determined by the relative sizes of the independent variables: clearance and Vd. Therefore, a reduction in Vd can be expected to decrease Kd 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 Vd), 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.
Slide 19	**Reparameterization** ● 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 	
Slide 20	**Reparameterization Turnover Model** $\frac{\mathrm{dPCA}}{\mathrm{dt}} = \mathrm{R_{syn}} - \ln(2)/\mathrm{T}half_{\mathrm{PCA}} \times \mathrm{PCA}$ Turnover of prothrombin complex activity (PCA) has a half-life of ($\mathrm{T}half_{\mathrm{PCA}}$) around 14 hours. This explains the delay in warfarin response. 	

Slide 21	# Not all Reparametizations are Equivalent  Vittal Shivva[1], Stephen Duffull[1] School of Pharmacy[1] University of Otago, Dunedin, New Zealand ● 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 	