TCP Transl Clin Pharmacol
2015;23(2):42-45
http://dx.doi.org/10.12793/tcp.2015.23.2.42

TUTORIAL

Clearance

Nick Holford[1]* and Dong-Seok Yim[2,3]

[1]Department of Pharmacology & Clinical Pharmacology, University of Auckland, Auckland, New Zealand, [2]Department of Clinical Pharmacology and Therapeutics, Seoul St. Mary's Hospital, [3]PIPET (Pharmacometrics Institute for Practical Education and Training), College of Medicine, The Catholic University of Korea, Seoul 06591, Korea

*Correspondence: Nick Holford; Tel: +64-9-923-6730, E-mail: n.holford@auckland.ac.nz

Received 21 Sep 2015
Accepted 4 Oct 2015

Keywords
clearance,
pharmacokinetics,
clinical pharmacology

pISSN: 2289-0882
eISSN: 2383-5427

This tutorial deals with basic concepts of clearance, the most important parameter in pharmacokinetics but often challenging for students in clinical pharmacology. Its relationships with dose, concentration and elimination rate are discussed using a physical model and examples of commonly used drugs, as well as its physiological aspects pertaining to the blood flow to differing organs. Finally, application of clearance to the calculation of maintenance dose rate and half-life is used to show how it is essential in pharmacotherapy and clinical pharmacology.

Clinical Pharmacology

What does pharmacology mean? Pharmacology is derived from a Greek word (pharmakon). The ancient Greeks used this word to mean a medicine, a poison or a magic spell. These 3 meanings apply today when we refer to a drug which is used for therapeutic benefit (medicine) which will always have associated adverse effects (poison) and sometimes may produce quite unexpected results (magic). The most obvious expression of magic is the placebo response.

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. However, it is believed to be the key 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).

The rational use of clinical pharmacology is to first decide on the desired target effect then use pharmacodynamic properties to predict the target concentration. With the target concentration it is then simple to calculate an appropriate loading dose (using V) and maintenance dose rate (using CL) to achieve and maintain the target.

Principles of Clearance

Clearance is the most important pharmacokinetic parameter for rational clinical pharmacology. This is because most drugs are often used on a regular basis and their effects can be linked to the average steady state concentration. The steady state concentration is determined only by clearance for any given dose rate. This is true if the bioavailability (F) of a dose is assumed to be 100% or equivalently, that clearance is the apparent clearance (CL/F) when the ratio of clearance to bioavailability is assumed to be constant.

The definition of clearance (CL) links drug concentration to the rate of elimination (rate out) (Fig. 1)

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

Figure 1. The definition of clearance

Note that elimination and clearance are NOT the same thing. Elimination describes the rate of loss (mg/h, amount per time), while clearance has units of flow (L/h, volume per time). If clearance is constant then the elimination of a drug will be linearly proportional to the drug concentration.

$$Rate\ Out = CL \cdot Concentration$$

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. There are often important differences between unbound, serum and blood concentrations. For all practical purposes there is no difference between plasma and serum concentrations.

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.[1] If the target concentration is known, what dose rate is needed to maintain the concentration at the target?

This can be easily determined for the steady state case when, by definition, the rate of drug input is equal to the rate of drug loss (elimination). The rate of drug loss at the target concentration of 10 mg/L is calculated using the clearance (3 L/h).

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. The maintenance dose rate needed to maintain the target concentration is therefore equal to the rate of drug loss (30 mg/h) at this concentration.

$$\begin{aligned} Rate\ Out &= Rate\ In \\ Rate\ Out &= CL \cdot Concentration \\ mg/h &= L/h \cdot mg/L \\ 30 mg/h &= 3\ L/h \cdot 10 mg/L \end{aligned}$$

Note the units of clearance are typically L/h and concentration is mg/L. Maintenance dose rates are therefore predicted with units of mg/h.

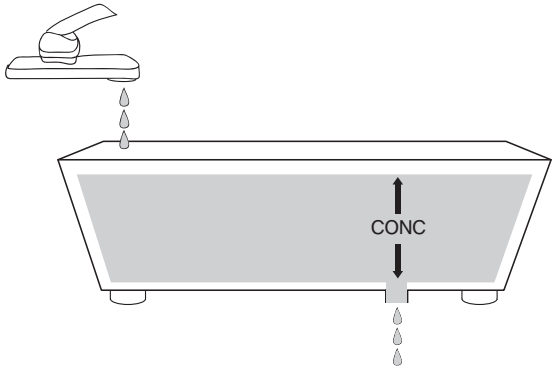

Figure 2. The bathtub model for clearance.

The Bathtub Model of Clearance

The bathtub provides a physical model to explain how clearance determines the rate of drug elimination (Fig. 2).

This bathtub has a constant rate of water flowing in from the tap (rate in = 3 drops/unit time).

Water is lost from the bathtub at the same rate (rate out = 3 drops/unit time) which keeps the bath water level constant (steady state).

Clearance is determined by the size of the plughole in the bathtub. The elimination rate of water is controlled by the clearance and the height of the water above the plughole.

Note that the volume of water in the bathtub does not affect the rate of elimination. The bathtub could be the size of a swimming pool but as long as the height of the water above the plughole and the size of the plughole are the same then the rate of water loss will not be changed regardless of the water volume changes.

Physiological Aspects of Clearance

Physiological explanations of clearance are usually based on blood concentrations so that the resulting blood clearance can be directly compared to organ blood flow. If the concentration of drug is the same in blood and in plasma then the clearances will be the same. However, if a drug concentrates in blood cells so that the blood concentration is times greater than plasma concentration (e.g. tacrolimus[2]) the blood clearance required to explain the same elimination rate will be smaller than plasma clearance. Conversely, if a drug does not penetrate well into blood cells the blood concentration will be lower (e.g. gentamicin[3]) than plasma concentration and the blood clearance will be higher than plasma clearance.

A key factor determining the size of clearance is the blood flow to an organ. The organ blood clearance cannot be any bigger than the organ blood flow rate. Note that blood clearance and blood flow are in the same units of volume/time (usually expressed as L/h) so they can be directly compared.

The liver is the largest single organ responsible for drug clearance. It has a typical blood flow of 90 L/h/70 kg. The main clearance mechanism by the liver is enzyme metabolism but some drugs are also excreted unchanged in the bile. Biliary excretion does not necessarily mean elimination because drug excreted in the bile can be re-absorbed in the small intestine.

The kidneys together have a combined blood flow of 70 L/h/70 kg but few drugs have blood renal clearance approaching renal blood flow. All drugs (except for some large protein molecules) are filtered through the glomerulus but most are reabsorbed either passively or by active uptake mechanisms. Polar molecules are not readily re-absorbed and so are extensively excreted in the urine. The upper limit on renal clearance by glomerular filtration is the glomerular filtration rate (6 L/h/70 kg). Some

TCP
Transl Clin Pharmacol

molecules e.g., weak acids like penicillin, are actively secreted by the tubules and can have clearances approaching renal blood flow.

Clearance of Common Medicines

Glyceryl trinitrate is used to treat angina. It is a very unstable molecule (it is an explosive when formulated differently as dynamite). It breaks down in many tissues of the body and its clearance is not limited by blood flow to a single organ. It is volatile even in tablet form, which means care has to be taken with the kind of container and its storage.[4]

Morphine is metabolized extensively in the liver and its blood clearance (60 L/h/70 kg) approaches liver blood flow. For this reason one can predict it will be extensively extracted from the blood as it passes through the liver.

Gentamicin is eliminated mainly by glomerular filtration so its clearance is about 6 L/h. It has a low renal extraction ratio.

Digoxin is cleared both by glomerular filtration but also by metabolism in the liver. The extraction ratio for both organs is low.

Theophylline is mainly metabolized by the liver but its blood clearance is low in relation to liver blood flow (blood to plasma ratio is close to 1.[5] Only a small fraction is extracted as blood passes through the liver. Renal elimination of theophylline is negligible.

Warfarin has very slow clearance by liver metabolism and therefore a very low hepatic extraction ratio.

Classification of Clearance

Clearance processes can be classified depending on whether clearance is constant (i.e., apparently independent of concentration or organ blood flow) or varying (i.e., with changes in concentration or organ blood flow. In this context, clearance is considered constant within an individual.

Concentration independent clearance is described by a first-order elimination process while concentration dependent clearance is a mixed order elimination process.

Concentration independent, concentration dependent and flow dependent clearance are not exclusive properties. A drug can be eliminated by a combination of these processes.

Note that although first-order clearance is constant the rate of elimination still varies with concentration.

When clearance is constant (apparently independent of concentration or organ blood flow) then synonyms for the elimination process are first-order and linear.

Glomerular filtration is always a first-order process.

Most drug metabolism can be approximated by a first-order process because concentrations are small in relation to the Km.

When clearance depends on drug concentration, the elimination process is called mixed-order. Synonyms are non-linear and Michaelis-Menten elimination.

Renal tubular secretion of penicillin is an active process that is saturable and thus it is mixed-order.

Metabolism of phenytoin (a commonly used anticonvulsant) is saturable at doses close to those used clinically.

The order of a chemical reaction can be defined in terms of the number of reactive species determining the rate of the reaction.[6]

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).

$$Rate\ Out = \left[\frac{Vmax}{Km+c}\right] \cdot C$$ Mixed order

$$Rate\ Out = CL \cdot C$$ First Order when C<<Km

$$Rate\ Out = Vmax \cdot C$$ Approaches zero-order when C>>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.

The elimination of digoxin is a first-order process. The target concentration of digoxin (2 μg/L) is very small in relation to the Km of enzymes involved in its hepatic metabolism.

On the other hand, the concentration of ethanol at a legal driving limit (e.g., 500 mg/L) is much larger than the Km for ethanol (63 mg/L; [7]), so it has mixed order elimination. At higher concentrations, first-order elimination processes (urine, breath) contribute to overall ethanol elimination. Observed ethanol elimination is never zero-order although this assumption is often made (incorrectly) for forensic purposes.

When clearance is flow dependent it is usually associated with elimination by the liver. Morphine is an example of a drug with clearance dependent on blood flow. If morphine is given to patients with heart failure, the liver blood flow is reduced because of heart failure and so clearance can be quite low. This means the maintenance dose should be reduced.

Clinical Applications of Clearance

The main clinical application of understanding about clearance is for prediction of the maintenance dose rate.

$$Maintenance\ Dose\ Rate = CL \cdot Target\ Concentration$$

A second useful application is the ability to calculate the half-life. This requires the volume of distribution (V) to be known as well as clearance.

$$T_{1/2} = \frac{0.7 \cdot V}{CL}$$

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.[8]

Adsorption of drug in the gut by activated charcoal can enhance elimination by preventing primary absorption and reabsorption 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.

Conflict of interest

The authors have no conflict of interest.

References

1. Holford N, Black P, Couch R, Kennedy J, Briant R. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? A randomised concentration-controlled trial. Clin Pharmacokinet 1993;25:495-505.
2. Størset E, Holford N, Hennig S, Bergmann TK, Bergan S, Bremer S, et al. Improved prediction of tacrolimus concentrations early after kidney transplantation using theory-based pharmacokinetic modelling. Br J Clin Pharmacol 2014;78:509-523.
3. Lee MG, Chen ML, Huang SM, Chiou WL. Pharmacokinetics of drugs in blood I. Unusual distribution of gentamicin. Biopharm Drug Dispos 1981; 2:89-97.
4. Marty J, Shaw J, Hunt D. The stability of glyceryl trinitrate tablets during patient use. Aust N Z J Med 1983;13:147-150.
5. Ferron LA, Weber JP, Hébert J, Bédard PM. Theophylline concentrations in serum, plasma, and whole blood compared. Clin Chem 1985;31:1415-1416.
6. Wikipedia. Order of reaction. 2015.
7. Holford N, Jiang Y, Murry DJ, Brown TL, Gary Milavetz G. The Influence of Body Composition on Ethanol Pharmacokinetics using a Rate Dependent Extraction Model. PAGE 2015;24:3405. [www.page-meeting.org/?abstract =3405]
8. Cutler RE, Forland SC, Hammond PG, Evans JR. Extracorporeal removal of drugs and poisons by hemodialysis and hemoperfusion. Annu Rev Pharmacol Toxicol 1987;27:169-191.