

Fundamentals of Clearance

A Course on Physiologically Based Pharmacokinetic (PBPK)
Modeling in Drug Development and Evaluation

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Center for Human Health Assessment
Center for Drug Safety Sciences



Clearance concepts in physiology and pharmacokinetics

Background: Clearance terminology has a long history in describing both the physiology of specific organs and compartmental pharmacokinetics. These concepts also underlie most of the equations used in PBPK models.

The kidney removes drugs from circulating blood by filtration. The liver removes drugs from circulating blood by metabolism. With each of these organs, we can describe the function of the organ in terms of “clearances”. In this usage, clearance is a volumetric flow of blood (e.g., liters/hour) from which all drug is removed.

Kidney clearance

For the kidney, urinary clearance (Cl_{urine}) is estimated by the ratio of the total amount of drug excreted in the urine over a given time interval divided by the blood concentration and duration of collection.

$$Cl_{\text{urine}} = ((C_{\text{urine}} * \text{Urine Volume}) / C_{\text{blood}}) / \text{Collection Duration}$$

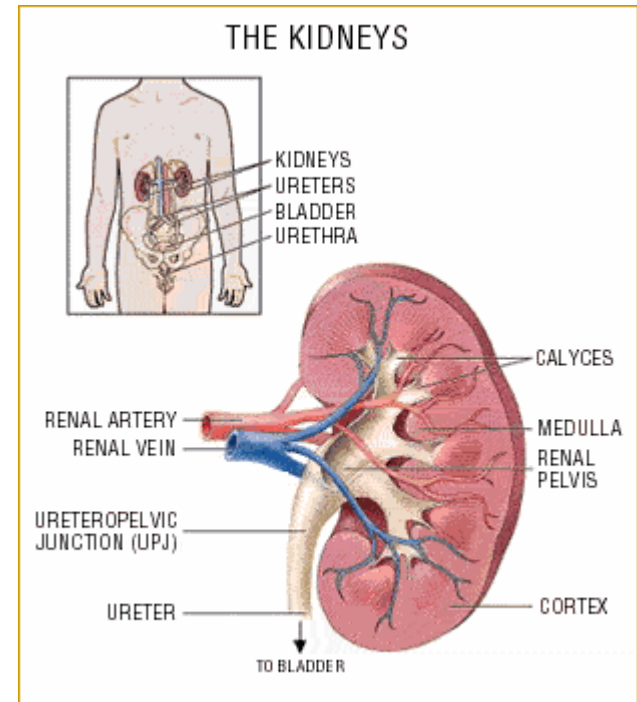
$$\text{Amount Removed} = Cl_{\text{urine}} * C_{\text{art}}$$

Thus, urinary clearance becomes the volumetric flow of blood from which the drug would have to be completely removed to account for the observed excretion into the urine. Compare renal clearances with renal blood flow and glomerular filtration to assess mechanisms of clearance – passive filtration vs. active transport.

Extraction of drug from renal blood flow

Another useful concept is extraction, i.e., the proportion of blood flow from which all chemical is removed during a single pass through the organ.

From the example with the kidney, extraction can be related to clearance and blood flow to the kidney (Q_{kidney}).



$$\text{Extraction (E)} = \text{Cl}_{\text{urine}} / Q_{\text{kidney}}$$

Hepatic clearance

A great deal of work and analysis has been conducted to describe the removal of drugs and toxicants by metabolism in the liver in relation to extraction and clearance. The major relationships are similar to those for the kidney.

$$Cl_{liver} = Q_{liver} * \text{Extraction}$$

$$Cl_{liver} = Q_{liver} * (C_{ART} - C_{VEN}) / C_{ART}$$

$$Cl_{liver} = Q_{liver} * (C_{IN} - C_{OUT}) / C_{IN}$$

$$\text{Amount Removed} = Cl_{liver} * C_{art}$$

Hepatic metabolism

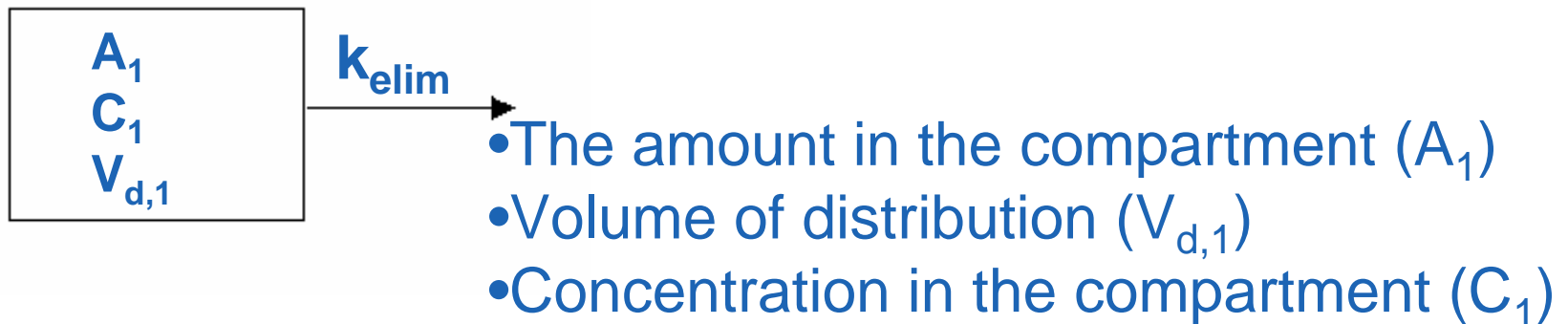
For the case where extraction is due to metabolism, the clearance at low substrate concentrations is readily expressed in relation to liver blood flow and the kinetic parameters for metabolism, V_{\max} and K_m .

$$Cl_{\text{liver}} = (Q_{\text{liver}} * V_{\max} / K_m) / (Q_{\text{liver}} + V_{\max} / K_m)$$

As with the kidney, the interpretation of the liver clearance is the volumetric flow which the drug has to be removed to account for the extraction.

Clearance concepts in data based compartmental PK models

In deriving the parameters from compartmental pharmacokinetic models, we also talk about clearance of compounds from the central compartment by the liver metabolism. A one-compartment model with metabolic elimination in the liver is expressed in terms of:



Clearance are related to volumes and flows

The mass balance equation for the change in amount in the compartment can be written in several equivalent forms.

$$dA_1/dt = - k_{elim} * A_1$$

$$dA_1/dt = - k_{elim} * V_{d,1} * C_1$$

$$dA_1/dt = - Cl_{liver} * C_1$$

So, clearance is the volume of distribution times and elimination rate constant.

Some advantages to assessing clearances in compartmental models

In the last formulation, the loss of chemical from the system over time is liver clearance multiplied by the concentration in the central compartment. If there are other organs that are involved in removal, *i.e.*, in filtration by the kidney or in exhalation by the lungs, the equation is simply altered to account for the sum of all the clearances.

$$dA_1/dt = - (Cl_{liver} + Cl_{kidney} + Cl_{exhalation}) * C_1$$

Clearance relationships as the foundation of PBPK models

When writing the mass balance equations for PBPK models, the individual terms on the right side of the equation, *i.e.*, the arrows in the schematics, are generally written in relation to compartmental concentrations, not amounts as done with the compartmental descriptions. The concentration terms in the equation represent “free” concentrations within the compartments.

What do these equations represent?

This structure for the models is equivalent to calculating the activity of drug available for diffusion, reaction, binding, or any other drug interaction that should be based on the free concentration of the compound in the compartments.

Some representative equations we use in this course are:

$$dA_{\text{liver}}/dt = Q_{\text{liver}} * (C_{\text{ART}} - C_{\text{L}}/P_{\text{L}}) - (k * V_{\text{liver}}) * C_{\text{L}}/P_{\text{L}}$$

$$dA_{\text{fat}} / dt = PA_{\text{fat}} * (C_{\text{VF}} - C_{\text{F}}/P_{\text{F}})$$

$$dA_{\text{fat blood}}/dt = Q_{\text{fat}} * (C_{\text{ART}} - C_{\text{VF}}) + PA_{\text{fat}} * (C_{\text{F}}/P_{\text{F}} - C_{\text{VF}})$$

All the proportionality constants in these equations have units of flow (volume/time)

$Q_{\text{liver}} ; Q_{\text{fat}}$

are blood flows (l/hr)

V_{max}/K_m

has units of mg/hr divided by mg/l
(i.e., liters/hour)

PA_{fat}

has units of a permeation
coefficient (cm/hr) times an area (cm²)
– vol/time

$k * V_{\text{liver}}$

has units of inverse time multiplied
by volume (volume/time)

How do we interpret these proportionality constants in the equations?

- They represent inter- and intra-compartmental clearances.
- Each clearance term represents the net volume of the compartment cleared of chemical by the individual processes, i.e., flow, diffusion, and first-order or saturable metabolism.
- It is perfectly reasonable to think of these mass balance equations as clearance equations that calculate net mass fluxes between and within compartments.
- The net organ clearances are determined by the interrelationship of these individual microscopic clearance terms for any particular compartment in the PBPK model.