Non-Linear Elimination

Guangda Ma

Auckland Pharmacometrics Group
Department of Pharmacology & Clinical Pharmacology
The University of Auckland
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Revision
Clearance and Elimination
• Elimination describes irreversible loss of the drug from the body

• Clearance describes the relationship between the rate of elimination and concentration.
  \[ CL = \frac{\text{Rate Out}}{\text{Concentration}} \]

• This can also be thought of as a measure of an organ’s efficiency at eliminating drug.
  \[ CL = Q \cdot \frac{C_{\text{venous}}}{C_{\text{arterial}}} \]

Revision
First and Zero Order Kinetics
• We can describe absorption processes as being dependent or independent of concentration.
  • Zero Order: Constant amount is absorbed per unit time.

• First Order: Constant proportion of drug is absorbed per unit time.

Absorption processes can be described as first-order (dependent on concentration) or zero-order (independent of concentration).

For compartment models which describe the rate of elimination as a first-order process (\( \text{Rate Out} = CL \cdot C \)), a constant proportion of the concentration of drug is eliminated per unit time.
First-Order Elimination

- When elimination is described as first-order process, clearance is assumed to be independent of concentration (or organ blood flow).
- Clearance is constant

When elimination is described as first-order process, clearance is assumed to be constant, thus independent of concentration or organ blood flow. The rate of elimination is however concentration dependent. The figure on the right illustrates the increase in the rate of elimination with increasing concentration as well as the constant nature of clearance.

Glomerular filtration is an example of a first-order process. Gentamicin is mainly eliminated by glomerular filtration, the figure on the left illustrates the time course of gentamicin concentration.

Non-Linear Elimination

- The assumption that clearance is constant may not hold under certain conditions
- Processes that rely on proteins are saturable at high concentrations (e.g. eliminating enzymes, transporters, protein binding)
- Activity of proteins can be induced or inhibited
- Non-linear elimination occurs when clearance is dependent on concentration (variable rather than not constant).

The assumption that clearance is constant (independent of concentration) ignores the possibility that processes involved in elimination may become saturated (capacity limited).

Elimination processes which require proteins such as transporters or enzymes may be taken up by substrates so there are few free transporters, or enzymes available, furthermore cofactor may be depleted. Protein amount and/or activity may also be inhibited or induced. Therefore, when concentration is high and the elimination pathway becomes saturated, an increase in concentration no longer increases the rate of elimination. Clearance is no longer constant as processes such as metabolism or renal secretion are capacity limited.

The implications of non-linear elimination for dosing and drug therapy means that small increases in dose can result in large increases in concentration, and that the time to elimination will differ with the rate of input.

Note non-linear kinetics is not exclusive to elimination. Non-linear kinetics mainly occurs in elimination processes as the enzymes and co-factors involved in drug metabolism (e.g. CYP450, n-acetyltransferase) may become saturated or depleted. Absorption and distribution processes may also exhibit non-linear kinetics (e.g. saturation of transport in gut wall, blood brain barrier transport).

Causes of Non-Linear Elimination

1. Saturation of elimination pathways
2. Induction of elimination pathways
3. Large Molecule Pharmacokinetics

There are many causes of nonlinear elimination. Three causes will be discussed in this lecture.

Metabolic clearance is the most common. This is because it is a capacity limited reaction in which the enzyme or its cofactor is not in limitless supply.
Substrate (S) binds reversibly to an enzyme (E) forming a substrate-enzyme complex (SE) which then reacts irreversibly to form metabolite (M) and enzyme:

\[ S + E \rightleftharpoons SE \rightarrow M + E \]

Michaelis and Menten describe the rate of enzymatic reaction (reaction velocity) to be related to:

- \( S \): substrate concentration
- \( V_{\text{max}} \): the maximum velocity of the system
- \( K_m \): concentration at which the reaction velocity is 50% of \( V_{\text{max}} \)

Reaction velocity:

\[ V = \frac{V_{\text{max}} \cdot S}{K_m + S} \]

Considering reaction velocity as the rate of elimination (or metabolism):

\[ \text{Rate of Elimination} = \frac{V_{\text{max}}}{K_m + C} \]

Saturation of Metabolic Clearance

When concentration is low, \( C \approx K_m \ setIs negligible relative to \( K_m \).

\[ CL = \frac{V_{\text{max}}}{K_m} \] and elimination is limited by concentration rather than metabolic capacity. Thus, the rate of elimination can be approximated by first-order kinetics (Rate = CL \cdot C).

In the figure first-order elimination (concentration-dependent) is illustrated by the blue dashed line. The red line illustrates the rate of elimination as a function of concentration (Rate = \( \frac{V_{\text{max}}}{K_m + C} \)), as concentration increases the assumption of linear clearance (independent of concentration) no longer holds.

When concentration is much greater than \( K_m \), elimination processes (e.g. metabolism, renal secretion) approach the capacity limit \( (V_{\text{max}}) \) as enzymes become saturated. Since \( K_m \) is negligible relative to \( C \), the rate of elimination occurs at a constant rate \( (V_{\text{max}}) \) that is close to the maximum elimination rate. The rate of elimination is thus approximately zero-order (independent of concentration), however, in reality concentrations are never high enough to produce zero-order elimination (this requires concentrations to be infinite). The use of pseudo-zero order elimination is an approximation that is sometimes seen in the literature but is often misleading (Holford NH. Clinical pharmacokinetics of ethanol. Clin Pharmacokinet. 1987;13(5):273-92.).

Concentrations that are neither small nor large in relation to \( K_m \) 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.

For drugs which follow linear kinetics, the elimination half-life is constant (independent of with dose or concentration). For drugs which follow non-linear kinetics, elimination half-life and clearance will not be constant, but rather dependent upon dose and concentration.

Further Reading Chapter 9 (Nonlinear Pharmacokinetics) in Applied Biopharmaceutics & Pharmacokinetics, Sixth Edition (Shargel L, Wu-Pong S, & Yu A)
**Ethanol**

- Excreted unchanged in breath, urine and sweat
- Hepatic metabolism by 2 enzyme systems (ADH, MEOS)
  - relative contribution of each system uncertain
  
  $$CL_{TOTAL} = CL_{HEPATIC} + CL_{RENAL} + CL_{OTHER}$$

  Elimination Rate = \( \frac{V_{\text{max}} \cdot C_p}{K_m + C_p} + (CL_{RENAL} + CL_{OTHER}) \cdot C_p \)

  - Initial exponential decay
  - Redistribution after infusion cessation.
  - Linear second phase
    - Concentrations >> \( K_m \) (80mg/L)
    - Constant amount removed per unit time.
  - First order third phase
    - Amount removed per unit of time changes with concentration

Further Reading:

**Induction of Elimination**

- Drugs can induce their own metabolic pathways (autoinduction) or metabolic pathways of other drugs (heteroinduction).
- Induction of enzymes occurs over several weeks
- Autoinduction may be described using a feedback model.
- Heteroinduction may be described using a turnover model.

Some drugs may induce enzymes or transporters involved in their own elimination (autoinduction) or induce enzymes involved in the elimination of other drugs (heteroinduction). This induction may increase enzyme amount and/or activity.

Induction of metabolic enzymes is time-dependent so requires repeated dosing to be observed and for the changes to reach steady-state.

Autoinduction can be described using a model which involves feedback between concentration and clearance; a higher concentration of drug will result in an increase to the enzyme pool and increase it’s clearance. Therefore, the level of enzyme should change with respect to concentration.

The figure on the left uses an one-compartment model to describe drug disposition, with input function, \( f(\text{input}) \), and inducible clearance described as a function of time, \( CL(t) \).

The amount of enzyme in the body is described using a turnover model. The concentration of drug in the central compartment increases the production rate of enzyme (\( k_{in} \)), thus changes in the pool (amount) of enzyme in the body affects the clearance function, \( CL(t) \). Note, drug concentration can drive an increase in enzyme transcription and translation (i.e. expression or synthesis), and/or reduction in the enzyme loss.

In contrast to autoinduction, where the concentration of drug induces a change in the pool of enzyme responsible for its own metabolism leading to a change in it’s own clearance, heteroinduction is less elaborate. A feedback model is not required as the inducing drug (e.g. phenobarbital) alters the amount of enzyme which is responsible for the metabolism of another drug (e.g. nortriptyline). The figure on the right illustrates such a turnover model, phenobarbital will stimulate the enzyme production rate (\( k_{in} \)), thus at steady-state, the amount of nortriptyline metabolising enzyme will have increased.

An understanding of mixed-order kinetics can help avoid dosing a drug at a concentration near enzyme saturation.

Ethanol is excreted unchanged in breath, urine and sweat, but undergoes hepatic metabolism, thus clearance from each pathway is additive to give CL_{TOTAL}.

Models can be used to describe the clearance pathways at each organ. These may or may not be linear. Ethanol elimination can thus be described by a system which describes elimination at the kidneys (CL_{RENAL}) and through the sweat and breath (CL_{OTHER}) using first-order processes and clearance at the liver (CL_{HEPATIC}) as a saturable process (since \( K_m \) is often surpassed due to the large doses taken).

The concentration-time curve shows three obvious phases. The top of the curve has an exponential decay; this is due to rapid redistribution of ethanol following cessation of the infusion. In the second phase, (pseudo-zero order) concentrations are well in excess of the \( K_m \), and the amount removed per unit of time is approximately constant. As concentrations get lower we see first-order kinetics emerge where the amount removed per unit of time changes with concentration (a linear relationship between concentration and rate of elimination).

Note that mixed order elimination occurs at all concentrations, the \( K_m \) (80 mg/L) is not a switch at which point the kinetics change but rather we see a gradual slowing of the rate of elimination with increasing concentration.

Note that it is difficult to estimate individual \( K_m \) and \( V_{\text{max}} \) for the two hepatic metabolism enzyme systems; alcohol dehydrogenase (ADH), microsomal ethanol oxidizing system (MEOS). A shared \( K_m \) and \( V_{\text{max}} \) seem to work just as well when describing ethanol elimination.

Further Reading:


### Induction of Elimination

**Rifampicin**

\[
\text{Dose} \times F_{D0} \times (1 + \frac{\text{EDS}_0 \times (\text{Gen} - 450)}{\text{EDS}_0 \times (\text{Gen} - 450) + 450})
\]

The feedback model used to describe autoinduction in the previous slide has been used to model rifampicin, an antibiotic used in the treatment of tuberculosis. It is metabolised at intestinal wall and actively excreted into the bile at liver. Rifampicin is one of the most potent inducers of the cytochrome P450 system and will cause its own metabolising enzymes to become induced during the first few weeks of therapy. A decrease in rifampicin exposure with time with repeated dosing has been reported. The dose dependent absorption of rifampicin, coupled with the capacity limited elimination means patients receiving high doses are at risk of overdosing. Contrasting that is the auto-induction of metabolism that could lead to sub-therapeutic concentrations and treatment failure should it not be accounted for in the first weeks of therapy.

**Further Reading:**


Target Mediated Drug Disposition

- Target receptor binding often happens quickly and at low concentrations
  - Targets are in high supply and mAb binds with high specificity and high affinity
- Once bound, receptor and mAb complex are internalised for cell membrane bound receptors, and broken down for cytosolic receptors
- Target Mediated Drug Disposition (TMDD) tends to be:
  - visible at low concentrations (at high concentrations linear elimination dominates, target binding is saturated)
  - results in faster than linear elimination alone
  - Nonlinear elimination will increase when mAb targets are increased
  - Targets will saturate

Most mAbs bind with high affinity (they have a low $K_d$, the equilibrium dissociation constant: $K_d = K_{on}K_{off}/K_{eq}$). This is done by designing the mAbs to dissociate slowly (so $K_{off}$ is small). $K_d$ is inversely related to affinity, i.e. when $K_d$ is low, affinity is high. The half-life for dissociation can range from a matter of minutes through to several days. Further complicating these kinetics is immunogenicity: mAbs are foreign to the body and so may stimulate an immune response from the patient depending on their genetics, disease, etc. This may be large or minor. Response typically includes production of anti-drug antibodies that can bind the mAb to either inactivate it or clear it. FcRn (or the Brambell receptor) is a pathway designed to protect IgG from phagocytosis and subsequent catabolism and acts to return IgG complexes to the extracellular fluid. This can also alter the internalization (or recycling back out of the cell) for mAbs. These various factors illustrate the complex roundabout of mAbs in the body, making TMDD a difficult pharmacokinetic problem.

A general model for TMDD includes elimination of drug from the plasma as the combination of first-order elimination from the central compartment, specific target binding (followed by internalization into the cell where it is broken down) and turnover of the target.

This figure illustrates a one compartment ligand model coupled to target turnover and formation of ligand-target complex.

Input of ligand (drug) into the central compartment is described using an input function, $f$ (input); note that two-compartment models are often used in the literature, however a one compartment model is used here for simplicity. $k_{in}$ and $k_{out}$ are constants which describe turnover of the target (R). Unbound ligand in the central compartment will bind reversibly ($k_{on}$, $k_{off}$) to target forming a ligand–target complex (RL). There are therefore two routes by which the ligand may be eliminated, non-target mediated loss of unbound ligand ($k_{e(R)}$) and target mediated loss of the ligand-target complex ($k_{e(RL)}$).

The law of mass action allow for derivation of three ordinary differential equations to describe ligand (L), target (R) and target-ligand complex (RL).

\[
\frac{dL}{dt} = f \text{(input)} - k_{e(R)} \cdot L - k_{on} \cdot L \cdot R + k_{off} \cdot RL
\]

\[
\frac{dR}{dt} = k_{in} - k_{out} \cdot R - k_{on} \cdot L \cdot R + k_{off} \cdot RL
\]

\[
\frac{dRL}{dt} = k_{on} \cdot L \cdot R - RL(k_{off} + k_{e(RL)})
\]

This model is linear at very low and very high ligand (drug) concentrations. At low ligand concentrations, the target is not saturated so there will be two parallel first-order (linear) routes for ligand removal (non-specific clearance and elimination via the target). At high ligand concentration, elimination via the target becomes saturated so it's contribution to ligand clearance becomes limited.

Four phases of TMDD have been observed:

1. Initial distribution phase (drug and target equilibrate)
2. High concentrations so targets are saturated, drug is mainly eliminated by first-order elimination routes (apparent linear phase)
3. Concentrations low enough that the target receptors are not saturated. Drug is eliminated directly as well as in the form of the drug-target complex. Both target mediated CL and nonspecific linear CL dictate the profile.
4. Concentrations are low, target receptors are in high supply, elimination is a first-order process along with elimination as a drug–target complex.

Note ligand concentration in the figure is expressed in the log domain.

The full model makes several assumptions but can be easily adjusted and extended to reflect underlying physiology. It also has lots of parameters and so a fair amount of data is needed to estimate them all well. Approximations can be used when insufficient data exists to estimate all parameters.

One approximation (thus reducing the number of parameters) is to use Michaelis Menten kinetics. This may be suitable when the target concentration is small relative to the free drug concentration and so the target receptors saturate easily at clinical doses and we don’t need to capture the profiles at low concentrations relative to target receptors. Here we are not attempting to estimate the irreversible elimination of the ligand–receptor complex, instead we indirectly get a sense of it from the $K'_m$ parameter. $K'_m$ here is not directly comparable to traditional $K_m$ parameters because it does not just represent affinity but both affinity ($\frac{k_{on}}{K_m}$) as well as irreversible elimination of the ligand-target (RL) complex.

Further Reading:
