Pharmacokinetics

This document is intended to expand on the derivation of pharmacokinetic results, and use some of the more complex methods of calculating them. As a discussion on the principles, it may not always present the simplest way, nor will it be in the most logical order to calculate the quantities.

Dose

An IV bolus dose D is assumed to immediately enter the blood in entirety. Equilibrium with other compartments may take time.

An infusion will administer the dose at a steady rate R into the blood.

Other routes (oral, im, sc) will give a total dose of D.F, where F is the availability of the drug. This will be provided over a period of time. Where the drug is solid and dissolves at a fixed rate (e.g. sustained release oral, im or sc injections that precipitate) this will behave as an infusion – a constant rate of drug release over a given time. Rate R = D.F/T where T is the total time that the drug is released over. Where the drug remains in solution, the rate of absorption will be proportional to local concentration, in turn proportional to the amount (M) still present in the tissue.

$R = k_{in}M$ k_{in} is a constant
$dM/dt = -R$

$\Rightarrow M=M_0\exp\{-k_{in}t\}$ M_0 will typically be D.F, but cautious of where the loss of drug occurs (i.e. $M_0 > D.F$ for some situations)

Area Under Curve (AUC)

There are many ways of calculating AUC for a given plot.

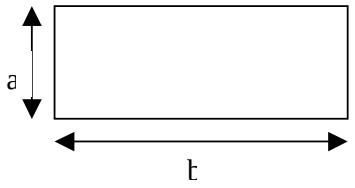
1. Single compartment model – applies for any region described by a single exponential (i.e. straight line on a semi-log plot). Integration of the concentration from time *t* to infinity gives $AUC = C_t/\lambda$. In the rare case that the concentration of a drug follows a single compartment model throughout, simply projecting back to t=0 (on semi-log plot) and applying this formula will give the total AUC. In most situations the earlier part of the curve will be more complex and a hybrid method will be required.

2. Geometric/hybrid method – will work for any curve, with accuracy depending on how the curve is divided.

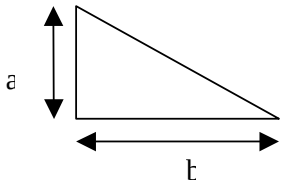
The curve is divided into sections approximating to rectangles, triangles, and trapezia. The area of each shape is calculated, and these areas are added together to give total AUC.

The method can be improved somewhat by using a hybrid of the geometrical and single compartment approaches. The semi-log plot is used to identify a time after which the drug concentration follows a single compartment pattern (i.e. approaches a

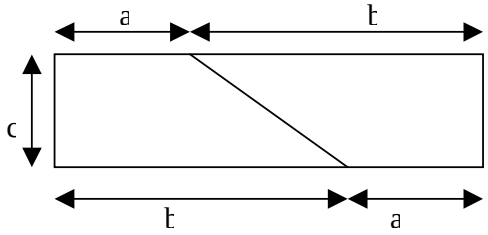
straight line on the plot). The area under the curve from this time onwards is calculated by C_t/λ as before, and the geometrical method used for earlier times.



Area = a.b



Area = a.b/2



Two identical trapezia back to back make a rectangle. Area of rectangle is (a+b).c, so area of a trapezium is given by (a+b).c/2

3. Curve peeling – useful in some situations, but more complex and less universal than the geometric approach. The method assumes the concentration can be modelled as the sum of two exponentials, such that $C = C_1\exp(-\lambda_1 t) + C_z\exp(-\lambda_z t)$ The values with subscript z are calculated from the terminal phase portion of the curve, and C is the actual, measured concentration at any particular time. By determining C_1 and λ_1 we find the total AUC by integrating C_1 and C_z separately with respect to t, and then taking the sum of these two values.

i) Plot semi-log graph of concentrations, use gradient at large values of *t* to determine terminal phase constant of elimination, λ_z.
ii) Project the terminal phase straight line back to t=0. Use this line to calculate theoretical actual concentrations (i.e. not logged) for the time points real data exists for.
iii) Calculate values of $C_1=C-C_z$ where C is the actual concentration at any given time, and C_z is the concentration calculated from the terminal phase.
iv) Construct a semi-log plot of C_1 against t, and determine the elimination constant from the gradient of this line at small values of *t*.
v) Use $AUC=C_1(t=0)/\lambda_1 + C_z(t=0)/\lambda_z$ to find total AUC.

Clearance

Clearance is the theoretical amount of plasma completely cleared of the drug per unit time. Usually it will be a constant, therefore as drug is eliminated (and so the plasma concentration drops), the rate of elimination will decrease. Clearance is given by dividing rate of elimination by plasma concentration.

$CL = R_e/C$

However, to calculate it we usually use AUC and D. We know that R_e.=C.CL Integrating both sides with respect to time, we find the left hand side gives us the total amount eliminated. This should be equal to the dose absorbed (=D.F). The right hand side will give CL.AUC, assuming that CL is constant. Hence D.F=AUC.CL and so:

CL=D.F/AUC

If F is not known, we can only calculate CL/F, and not the absolute value. As before, for an IV dose, F=1.

Availability

Availability, or fraction absorbed (F) is the proportion of a dose administered that actually ends up in the circulation. For an IV dose this is assumed to be all of the drug, so F=1 and is usually omitted. For other routes, F can be significantly lower.

To find F, we assume that clearance is constant regardless of route by which drug is given. By definition then, $CL = D_{IV}/AUC_{IV}$, but also $CL = D_{other}.F/AUC_{other}$ where other can be oral, im, etc. Setting these equal to each other:

$D_{IV}/AUC_{IV} = D_{other}.F/AUC_{other}$

Giving the same dose for each route, D cancels. By rearranging:

$F = AUC_{other}/AUC_{IV}$

Half life

Half life is most easily obtained from the rate constant for elimination, λ. Elimination follows exponential decay. In the terminal phase, this should be a single exponential with rate constant λ_z. $C=C_0\exp(-\lambda_z t)$. Taking natural logs gives $\ln(C) = \mathrm{Ln}(C0) -\lambda_z t$. If we plot ln(C) against t, the gradient gives $-\lambda_z$.

Half life ($t_{½}$) is the time for concentration to drop by half, i.e. to go from C_0 to $C_0/2$. Substituting into the exponential decay equation:

$C_0/2 = C_0\exp(-\lambda_z t_{½})$
$\Rightarrow ½ = \exp(-\lambda_z t_{½})$
$\Rightarrow -\ln(½) = \lambda_z t_{½}$
$\Rightarrow t_{½} = 0.69/\lambda_z$

Absorption

A similar method to the curve peeling used for calculating AUC can be used, provided absorption is more rapid than elimination. In this case, the terminal phase represents elimination only, and so the rate constant for elimination can be found, and then used to project back to earlier times, to give theoretical 'elimination only' concentrations C_0. We then plot values of C_0-C (again, as a semi-log plot), and the gradient of this line represents the rate constant for absorption.

If elimination is more rapid than absorption, the system can be treated as an infusion, with initial rate of administration equal to the initial rate of absorption.

Volume of distribution

The calculated volume of distribution will be a true value only when the drug has equal affinity for all compartments that it distributes through. In other cases, the calculated volume is the equivalent plasma volume required to account for the plasma concentration of drug seen.

The volume is calculated from the amount in the body, divided by the plasma concentration. The initial volume of distribution is simply:

$V_i = D.F/C_0$

This will usually reflect the plasma volume, unless the drug has a high affinity for the plasma proteins.

The steady state volume of distribution is the one frequently tabulated, and is:

V_{ss} = amount in body/C

We can also find the terminal phase volume of distribution. We know that clearance is a measure of the volume of plasma completely cleared of the drug per unit time, and is equal to the amount of drug in the body at time t_0 divided by the AUC from t_0 to infinity. AUC from t_0 is also given by C_0/λ_z. Combining these we find:

$$\text{Amount}(t_0) = CL.AUC(t_0)$$
$$= CL.C_0/\lambda_z$$

Amount at t_0 divided by C_0 gives the volume of distribution at that time, so:

$V_z = CL/\lambda_z$

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