Pharmacokinetics

Pharmacokinetics: the study of the characteristics of a drug's absorption into, distribution through, and clearance from the body.

To be able to predict fully the time course of the drug, we need to know:

Clearance (CL)
Half life ($t_{½}$)
Availability (F)
Dose given (D)

From these we can calculate other factors, such as volume of distribution, and maximum and minimum concentrations for a given dose schedule.

Notes

These values are used to determine concentration in a given compartment at a given time. They will not necessarily correlate directly with clinical effect.

The methods described below show one way of approaching problems. They are intended to be a fairly simple approach, and as such may not always be the most accurate. The results obtained should be reasonable however. There will be an additional set of notes giving more detail on the derivation of these formulae, and more accurate methods.

The seminar suggested two ways of plotting data logarithmically. Firstly by calculating natural logs (ln key on calculator) of the plasma concentrations and plotting on normal paper, or by plotting the raw data on semi-log paper. I would strongly advise the former – while it takes a little longer, it is generally harder to get confused with, and saves additional conversion steps later.

A) Determining Constants

Half life

Calculate natural logs of plasma concentrations, and plot these against time on normal (linear) graph paper. The plot should approach a straight line as it enters the 'terminal elimination phase'. When it does, the half life ($t_{½}$) is given by dividing ln(2) by the negative of the gradient. The negative gradient is called the elimination rate constant (λ_z)

$t_{½} = 0.69/ \lambda_z$

It is possible to confirm this on a linear plot (concentration against time) by selecting a suitable point, and finding the time at which the concentration has dropped by half. Doing this for three starting points and taking the average will provide a check on the value found, and is worth doing if time permits. Remember that this can only done for the terminal phase – i.e. use times for which the log plot has started to form a straight line.

Clearance

Clearance (CL) is the amount absorbed, divided by the area under the curve (AUC) on a linear plot. For an IV dose, the amount absorbed is simply the dose (D). For other routes of administration, the amount is the dose multiplied by the availability (F).

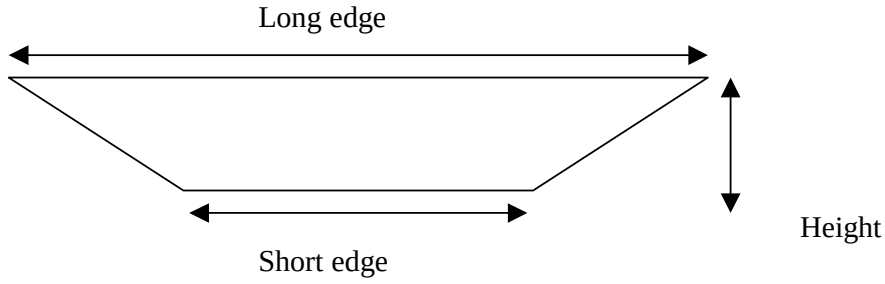
CL = D.F/AUC

The easiest and fastest way to find the AUC is to combine two methods

i) Numerical

Plot the concentration against time, and then divide the curve into simple geometric shapes – typically trapezia, with one or two rectangles or triangles. Work out the area of each shape, then sum these to get total AUC.

Rectangle – base.height
Triangle – ½.base.height
Trapezium – ½.(long edge+short edge).height



ii) Integration

The derivation of this can be tricky, but the application is simple. For the terminal elimination phase (i.e. the bit where we get a straight line on the plot of ln(concentration) against time), the AUC is given by:

$AUC = C_0/\lambda_z$ C_0 is the concentration at the start of the time we're integrating over

Remember that C_0 is the actual concentration, not the ln of it.

If the ln plot is straight at all times, then the integration method gives the correct answer quickly. If not, using the numerical method for the early part and integration for the later part may be helpful.

If you want to remember one method that will always work, just learn the numerical method – not always as fast or as accurate, but it will give a reasonable answer in every situation.

Volume of Distribution (V)

This can take several values, depending on what point is being considered. Typically we will want the steady state volume.

V_{ss} = Amount in equilibrium with plasma / C_{ss}

Terminal phase volume.

$V_z = CL/\lambda_z$

Initial volume of distribution is simply the dose divided by the initial concentration.

$V_i = D.F/C_0$

None of these are necessarily true volumes – will be influenced by affinity for different compartments. To illustrate this, consider a two compartment model, comprising 5l each of plasma and fat. If a drug binds equally to both compartments, we will find a 10l volume of distribution. If it has twice the affinity for fat as for plasma, then we will find a 15l volume of distribution.

Fraction Absorbed (F)

If not given in the question, this can be found by comparing the AUC for an IV dose with that for the administration route being considered.

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

Infusion

If an infusion is being given, then in the steady state rate of administration is equal to rate of removal, and so clearance is given by:

$CL = R/C_{ss}$ R is rate of infusion, C_{ss} is steady state concentration.

Half life can be calculated as above from data for the period immediately after the infusion has ended, or for the start of the infusion, by using C_{ss}-C instead of C in the plots.

B) Calculating Dose Regimes

Generally this is a matter of learning the formulae given in the seminar/lectures, and substituting numbers into them. The following are the ones I would consider to be most important, but this is my opinion only – don't take it as a fact.

Repeated doses

Average dose is given by considering the dose given, the interval, and the clearance. Note similarity to the equation for an infusion.

$C_{av} = DR.F/CL$ (DR is dose rate, i.e. D/τ where τ is the interval between doses)

Alternative form of this is:

$C_{av} = AUC/\tau$

The concentration will decay at a rate determined by λ_z between doses, so that:

$C = C_{start}\exp(-\lambda_z t)$

This gives the minimum concentration that will be reached between doses (immediately before the next dose is given), relative to the maximum (which will be immediately after each dose):

$C_{min} = C_{max}\exp(-\lambda_z \tau)$

The maximum is given by a calculation based on adding the effects of multiple doses, and works out as:

$C_{max} = (D/V_z)/[1-\exp(-\lambda_z t)]$

Loading dose is given by:

Loading dose $= D/[1-\exp(-\lambda_z \tau)]$

Infusion

The equation $CL = R/C_{ss}$ can be used to find C_{ss} for an infusion if CL has previously been found, e.g. from IV bolus dose data.

Loading dose $= C_{ss}V_{ss}$ (if V_{ss} given – use V_z if not)

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