Paper ST03

Statistics and Pharmacokinetics in Clinical Pharmacology Studies

Amy Newlands, GlaxoSmithKline, Greenford UK

ABSTRACT

The aim of this presentation is to show how we use statistics and pharmacokinetics (PK) in certain types of clinical pharmacology study. The focus will be on the statistical analyses of PK data, and we will give a brief description of PK and how we assess the PK of a compound. We will concentrate on two types of study design: First Time in Human (FTIH) and Repeat Dose. Also included in the presentation will be the objectives of these types of trial and when they happen in the drug development process.

The presentation will also give an overview of dose proportionality; as the dose increases, we expect that AUC (area under the concentration time curve) and C_{max} (Maximum concentration observed) increase in proportion, and will give a brief description of both the Power and ANOVA models. We will also look at accumulation i.e. whether the drug accumulates in the body, time invariance i.e. how the concentration profile at steady state compares to the full profile on Day 1 and how to perform an assessment of steady state using trough concentrations from the last 3-5 days of dosing to assess whether this has been achieved.

Example code will also be presented to show the statistical analyses of dose proportionality, using both the Power model and the ANOVA method for its assessment.

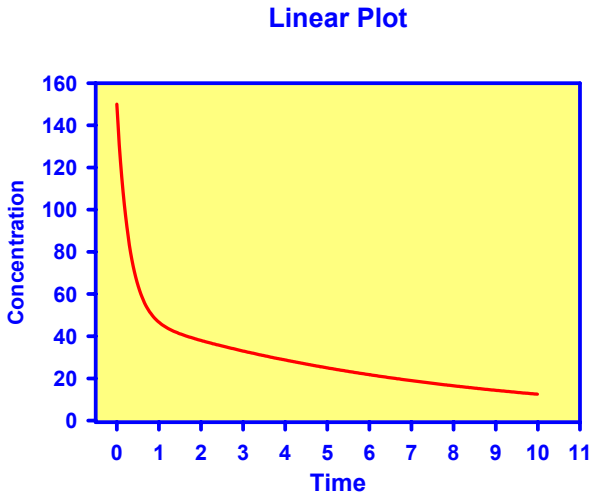
INTRODUCTION

Pharmacokinetics (PK) is particularly useful in the early phases of drug development. When considering a dosage regimen, we need to think about how the magnitudes of the therapeutic and toxic responses vary according to the dose given? We also need to think about how the magnitude of effect eventually declines with time, following single dose of the drug, and also what cost is incurred (i.e. the side effects, toxicity, and economics) with continuous drug administration.
This presentation will look at First Time in Human (FTIH) Studies and Repeat Dose studies. Since FTIH studies give a wide range of doses, which is an ideal opportunity for investigating dose proportionality. If the pharmacokinetics were proportional to the dose, this is to say that the concentration wherever it was measured (blood plasma etc) at any point in time was proportional to the amount of drug taken.
Repeat dose studies evaluate the safety and tolerability of single and repeat dosing. It gives an insight as to how the pharmacokinetics changes with repeat dose in comparison to single dose. Repeat dose studies give the opportunity to test for accumulation since multiple doses cause accumulation in the body. Accumulation occurs because the drug from previous doses has not been completely removed. We can also evaluate whether the pharmacokinetics of the drug remain unaltered after repeat administration i.e. the time invariance and we can also determine whether steady state has been achieved. If steady state has been achieved, the blood level of the medication after the patient has been taking it for a while should be fairly constant.

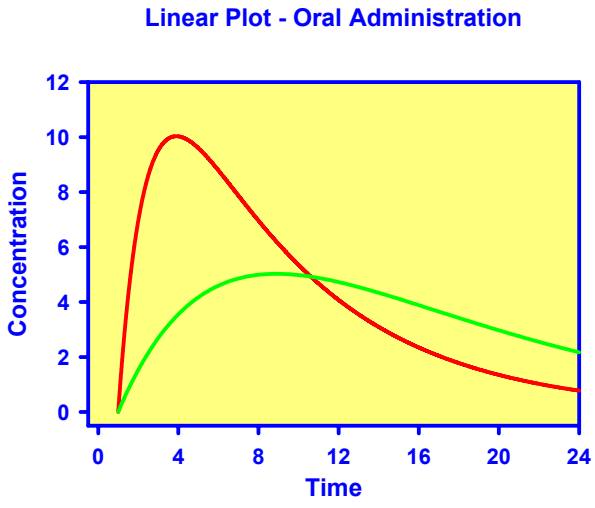
WHAT IS PHARMACOKINETICS

- The study of what the body does to the drug
- We are interested in ADME, the **A**bsorption (The disappearance of the compound from the site of administration), **D**istribution (The transportation of the compound to the rest of the body), **M**etabolism (The conversion of one molecule (parent) to another of other molecules (metabolites)) and **E**xcretion (The removal of the compound (parent or metabolite) from the body).

Typical Plasma PK Profiles after IV administration : Linear Plot in administration



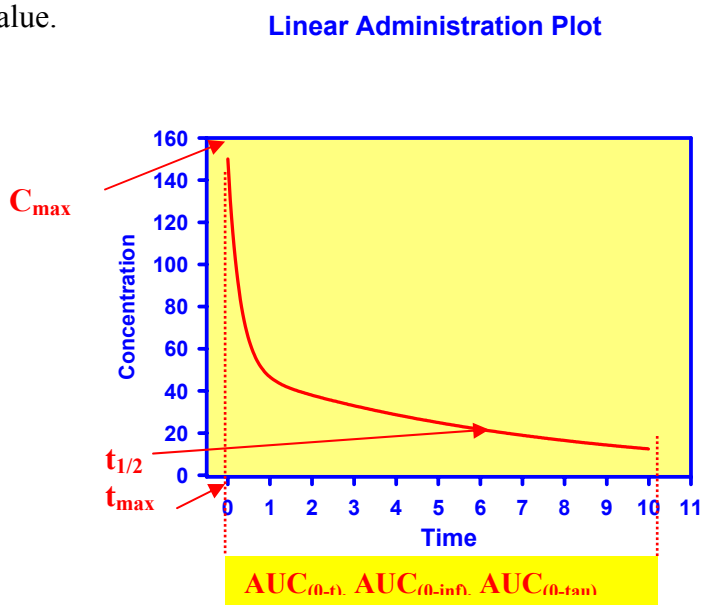
Typical Plasma PK Profile after Oral Administration: Linear Plot in administration



DESCRIBING THE PHARMACOKINETICS OF A COMPOUND

- C_{max}: Maximum concentration observed
- AUC – Area Under the Concentration – time curve

- $AUC_{(0-t)}$: AUC up to the last measurable concentration (otherwise called AUC_{last}). AUC is approximated by a series of trapezoids. Compute the area of all trapezoids and sum them to give the AUC up to the last sample drawn.
- $AUC_{(0-inf)}$: AUC curve to infinite time. As we cannot get the assays to go to infinity, we have to extrapolate to infinity. This can be calculated from the $AUC_{(0-t)}$ by the addition of a constant (C_{last}/λ_z), where C_{last} is the last observed quantifiable concentration and λ_z is the terminal phase rate constant.
- $AUC_{(0-tau)}$: AUC to the end of the dosing period (for example for OD dosing, the dosing tau is 24hrs.)
- t_{max} :Time at which the maximum concentration (C_{max}) is observed.
- $t_{1/2}$: Terminal phase half-life. The time it takes for the concentration levels to fall to 50% of their value.



ASSESSING THE PHARMACOKINETICS OF A COMPOUND

- Non-compartmental Analysis
  - Derived from plasma/serum PK concentration data without using modelling techniques.
- Compartmental Analysis
  - A model is assumed (for example the drug is distributed in a shallow compartment before excretion.)
  - The plasma/serum PK concentration data are modelled to obtain PK parameters.

TYPES OF STUDY DESIGN

1. FIRST TIME IN HUMAN
2. REPEAT DOSE

1. FIRST TIME IN HUMANS (FTIH)

WHY?

- To ensure the drug is safe and tolerable when given as a single dose into humans for the first time.
- To build a PK profile of each single dose of the drug (and perhaps conduct an initial assessment of the dose proportionality.)

TYPICAL DESIGN

- 4/5 periods per subject of single ascending doses with placebo interrupting.
- Healthy male volunteers.
- Ongoing safety and PK reviews between periods
- Sample size per cohort may be 8-12 subjects.
- 2/3 cohorts per study.
- Not usually formally powered for statistical testing

WHEN?

- When we have enough safety and tolerability information from pre-clinical studies to be able to safely proceed and predict the starting dose.

ENDPOINTS

- Safety: Adverse Events's, Electrocardiograms , vital signs, Labs
- PK: $AUC_{(0\text{-inf})}$, $AUC_{(0\text{-tau})}$, C_{max}, t_{max}, $t_{1/2}$
- PD endpoints, if applicable.

PRELIMINARY ASSESSMENT OF DOSE PROPORTIONALITY

- The Power Model: $\log(Y_{ijk})=S_i + P_j + \beta x \log(D_k) + \varepsilon_{ijk}$ where D is the total number of doses, N are the total number of subjects and P the total number of periods and i=1,….,N, j=1,….,P and k=1,…..,D. Y_{ijk} is the measured response variable, AUC or C_{max} on the kth dose, in the jth period, for the ith subject. S_i is the random subject effect for the ith subject, P_j is the fixed period effect for the jth period and ε_{ijk} is the error.
- Dose proportionality requires β to be close to unity for dose dependent parameters. The estimate of β together with appropriate confidence interval (β_L, β_U) can be used to quantify the degree of non-proportionality.
- A mixed effect model can be used to fit the Power Model
  -Response: $\log_e$-transformed C_{max} and $AUC_{(0\text{-inf})}$
  -Fixed effects: Sequence, period, $\log_e$-transformed dose (continuous variable)
  -Random effects: intercept for subject or both intercept and slope of log (dose) for subject maybe fitted as random effects.
  Of importance is to describe any major deviations from dose linearity and also to calculate whether doubling the dose results in a doubling of the AUC within the range studied.

SAS® Code for the Power Model to assess dose proportionality

```
proc mixed data=dataset ;

      class subject ;
      model log_pk_parameter= log_dose/ ddfm=kr /*ddfm selects the DF for F test
denominator DF for all F tests*/;
      random intercept log_dose /subject=subject type=UN gcorr s; /*This line
specifies that the covariance structure of the G matrix will be specified as
unstructured. This statement says that for a particular subject, there is some
correlation between the slope and intercept, (where log_dose is the slope).
Subject slope and intercept have been fitted as random effects.*/
       estimate 'Logdose - 1 unit' log_dose 1/cl alpha=0.1; /*This statement is
included to obtain the estimates of the mean slopes of the log_dose.*/
      ods output estimates=estimate;/*Gives the estimate of how the pk parameter
changes according to the dose of drug i.e the output from the estimate
statement*/
```

```
      ods output solutionr=solution;/*outputs the parameter estimates for the
random effects*/
run;
```

ANOVA METHOD FOR ASSESSING DOSE PROPORTIONALITY

- A reference dose should be chosen based on the lowest clinically relevant dose over which the pharmacokinetics can be adequately described. This is chosen by the kineticist and statistician jointly
  Following $\log_e$-transformation, dose normalised AUC and C_{max} will be analysed using a mixed model appropriate to the study design. Each dose will be compared with the reference dose on a pairwise basis. The geometric mean ratios for each dose level are compared to the reference dose. If the confidence intervals include unity, then there is no evidence to suggest the relationship between the test dose and the reference dose is not dose proportional. If the lower confidence interval lies only just below 1, this may be an indication that the true response at this level is slightly more than dose proportional compared to the reference dose level.
- If the power model has failed to converge and the ANOVA has become the primary analysis, dose proportionality will be concluded if 90% confidence intervals for dose normalised C_{max} and AUC are contained in the 80 to 125% range of the reference dose.
- A mixed effect model can be used to the ANOVA method:

-Fixed effects: sequence, period, regimen
-Random effects: subject(within sequence)

SAS Code for the ANOVA Model to assess dose proportionality

```
/* To compare all of the doses versus the reference dose */

data dataset1;
      set ardata.pk_dataset;
      if pk_parameter ne .;

       if pk_parameter in ( 'Cmax') ;

/* To calculate dose normalised  Cmax */
       dose_normalised_pk_parameter=(pk_value/dose)*100;
       log_normalised_pk_parameter=log(dose_normalised_pk_parameter);
run;

data cmax;
      set dataset1;
      if pk_parameter='Cmax';
run;

proc mixed data=cmax;
      class subject dose;/*Subject and dose have both been specified as
categorical*/
      model log_normliased_pk_parameter= dose / ddfm=kr; /*ddfm selects the DF
for F test denominator DF for all F tests*/
      random intercept /subject= subject ;
      estimate '60mcg vs 100mcg'  dose  1  -1 0  0  / cl alpha=0.1;/*These
estimate statements give the log of the ratios of each comparison listed in
quotes (since we are looking at the logged pk parameter). Notice we use dose
here, rather than logged dose, since it does not make a difference as we are
treating dose as a categorical variable.*/
```

```
      estimate '250mcg vs 100mcg'  dose 0  -1 1  0  / cl alpha=0.1;
      estimate '350mcg vs 100mcg' dose  0  -1 0  1  /cl alpha=0.1;
      lsmeans dose/diff cl alpha=0.10;/*Least squares mean option gives the
estimate of the mean for each dose, adjusting for all parameters in the model*/
      ods output estimates=estimatec ;/*Outputs the comparisons which have been
specified on the estimate statement*/
            lsmeans=lsmC;/*Outputs the least squares means from the lsmeans
statement*/
run;
```

2. REPEAT DOSE STUDIES

WHY?

- To find out if the drug is safe and tolerable when given repeatedly: usually for 10-14 days.
- To examine the PK of the drug after repeat dosing and compare to the PK after the single dose.
- If applicable, to examine the PD of the drug after repeating dosing.

TYPICAL DESIGN

- Either cross-over or parallel group design, double blind, randomised, placebo-controlled, 10-14 days of dosing, may be in patients or healthy volunteers.
- May have multiple regimens (QD, BID, TID) as well as different dose groups
- Generally dose escalate in dosing cohorts with the lowest dose being given first, and data review between cohorts.

WHEN

- Generally early in the drug development process, after the FTIH, or after a single dose study in patients.

ENDPOINTS - typically

- Safety: AEs, ECGs, Vital Signs, labs
- PK day 1: $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}tau)}$, C_{max}, t_{max}, $t_{1/2}$
- PK day 14 (last day): $AUC_{(0\text{-}tau)}$, C_{max}, t_{max}, $t_{1/2}$
- PD endpoints on first and last day if applicable

ACCUMULATION ASSESSMENT

- Rationale: Safety and Efficacy
- Multiple doses cause accumulation in the body.
- Accumulation is measured by R_0=$AUC_{(0\text{-}tau)}$ day 14/$AUC_{(0\text{-}tau)}$ day 1
- The observed accumulation ratio can be evaluated as follows in the analysis:

  Using a mixed effects model:
  -Response: log_e-transformed $AUC_{(0\text{-}tau)}$
  -Fixed effect: time
  -Random effect: subject

ASSESSMENT OF STEADY STATE

- When the rate of the drug input (eg Dose/hr) equals the amount of drug eliminated. Drug concentrations will fluctuate between the maximum (C_{max}, ss) and a minimum (C_{min}, ss) for as long as regular dosing occurs.
- Does the drug concentration get to Steady State?
- Use the trough concentrations from the past 3-5 days of dosing.
- The Steady State assessment can be made by using a mixed effect model with the following parameters:
  -Response: log_e-transformed Concentration

-Fixed effect: time (continuous variable)
-Random effect: Intercept and slope for time.

TIME INVARIANCE KINETICS

- We require to find out how the concentration profile at Steady State compares to the full profile on Day 1?
- This is similar to accumulation, but different denominators in the ratio:
- $Rs=AUC_{(0\text{-}tau)}$ Day 14/$AUC_{(0\text{-}inf)}$ Day 1
- A mixed effect analysis can be produced with
  -response: $\log_e$-transformed AUC
  -Fixed effect: time
  -random effect: subject

Conclusions

Here we have given a brief introduction to PK, and the different objectives of the First Time in Human studies, and the Repeat Dose studies.
We have also explored the differences between assessing dose proportionality using the power model, and the ANOVA method. The output is quite different from the two approaches, and quite often the ANOVA method is used as a back up to the power model. From the power model, we can estimate whether the slope of our doses is significantly different to 0. If this is the case, then we can conclude dose proportionality, (provided the data, when plotted, can confirm this). We can then use the estimate of the slope to predict what each subjects' value will be from the different dose. This gives an idea of whether we have dose response.
From the ANOVA method of assessing dose proportionality, we get adjusted means estimates for each of the doses, and then pair-wise comparisons for each dose to a reference dose. The ANOVA method shows which doses increased in a more than dose proportional manner, or otherwise.

References

GlaxoSmithkline SOP-CPK-0001 Standard Methods for the Non-compartmental Analysis of Pharmacokinetic Data
GlaxoSmithkline SOP-BMD-4002 Standard Statistical Methods for the Analysis of Pharmacokinetic Data
GlaxoSmithkline SOP-CPK-0007 SOP for the Non-Compartmental Data Analysis and Reporting of Repeat Dose Studies
GlaxoSmithkline SOP-CPK-0008 SOP for the Non-Compartmental Data Analysis and Reporting of Dose Proportionality Studies

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Brown H, Prescott, R. *Applied Mixed Models in Medicine.* first ed. West Sussex:John Wiley and Sons Ltd; 1999.

http://www.fda.gov/cder/guidance/index.htm

Contact Information

Amy Newlands
GlaxoSmithkline
Research and Development
Building 1 CPSP
Greenford Road
Greenford
Middlesex
UB6 0HE
e-mail:amy.h.newlands@gsk.com