Population Pharmacokinetics
and Pharmacodynamics
as a Tool in Drug Development

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Pharmacokinetics and Pharmacodynamics
Clinical Pharmacokinetics

Pharmacokinetics

Dosage Regimen → Plasma Concentration → Site of Action

Pharmacodynamics

Effect
Fig. 8-1. Distribution of doses of warfarin in 200 patients during chronic therapy. (Data from Koch-Weser.)
Fig. 7–6. Isoniazid concentration in plasma, 6 hr after oral administration of the same dose to 267 individuals. (Data from Evans, Manely and McKusick.)
Models
The type of model to be developed should be driven by the available information and the goal of the simulations.
\[ C(t) = C_1 \cdot e^{-\lambda_1 t} + C_2 \cdot e^{-\lambda_2 t} \]
\[ V_1 \cdot \frac{dC_1(t)}{dt} = -k_{12} V_1 C_1(t) - k_{10} V_1 C_1(t) + k_{21} V_2 C_2(t) \]
\[ V_2 \cdot \frac{dC_2(t)}{dt} = k_{12} V_1 C_1(t) - k_{21} V_2 C_2(t) \]
\[ Kp_H \cdot V_H \cdot \frac{dC_{out,H}(t)}{dt} = Q_H \cdot C_A(t) - Q_H \cdot C_{out,H}(t) - CL_{int} \cdot Kp_H \cdot C_{out,H}(t) \]
Pharmacokinetic Study Design
POPULATION
PHARMACOKINETICS/
PHARMACODYNAMICS

Estimating the pharmacokinetic/pharmacodynamic similarity and differences between individuals from measurements of drug levels in biological fluids (often blood) and pharmacological effect of subjects or patients arising from some population of interest
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Classical pharmacokinetic/pharmacodynamic study
numbers are small
subjects are homogeneous - often volunteers
studies are well controlled - experimental
sufficient data per individual
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Population study
- numbers are large
- subjects are heterogeneous - often patients
- study control is difficult - maybe multicentre observational
- sparse data
Sparse Data
1731 doses
322 concentrations
Tobramycin study

**Objective:** to establish dosage regimen guidelines to maintain maximum efficacy \((C_{\text{max}} > 6 \text{ mg/L})\) and minimum toxicity \((C_{\text{av}} < 4 \text{ mg/L})\) in a majority of patients

**Patients:**
- \(n\): 97 (after pruning)
- body weight (kg): 42-120
- age (yr): 16-85
- sex (M/F): 52/45
- creatinine clearance (ml/min): 10-166
- indication: variety of infection

**Study design:** no design - routine TDM
- dosage: 20 to 140 mg every 8 to 24 hr
- number of concentrations per individual: 1-9 (median 2)
- duration of therapy: 14 to 520 hr
Intelligent Analysis of Unavailable Data


“The inexperienced or naïve analyst might perceive the lack of data to be a minor handicap. The fact of the matter is that a superfluity of data is extremely confining, imposing extreme constraints on the technique, imagination and creativity of the analyst. On the other hand, a lack of data permits full exercise of one’s talents and abilities. The ideal situation is to have absolutely no data available at all”.
Why?

• It seeks to obtain relevant pharmacokinetic information in patients who are representative of the target population to be treated with the drug

• It recognizes variability as an important feature that should be identified and measured during drug development and evaluation

• It seeks to explain variability by identifying factors of demographic, pathophysiological, environmental or drug-related origin that may influence the pharmacokinetic behavior of a drug

• It seeks to quantitatively estimate the magnitude of the unexplained variability in the patient population
Warfarin study

Objective:

to predict warfarin maintenance dose requirements to achieve a desired degree of anticoagulation based on measurements obtained after a single dose of warfarin

Data:

n  48 normal subjects
weight (kg)  66-75
age (yr)  20-27
sex  male

Study design:

25mg single dose of racemic warfarin
14 blood samples (0-168 hr)

Measurements:

R and S warfarin (HPLC)
Prothrombin time (Quick one stage)
Factor VII (chromogenic method)
<table>
<thead>
<tr>
<th>Hours</th>
<th>Concentration (mg/L)</th>
<th>% Activity</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>1.0</td>
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<tr>
<td></td>
<td>100</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The graph shows the relationship between the concentration of a substance and its activity over time.
PHARMACODYNAMIC MODEL

rate of change = rate of clotting - rate of clotting of clotting activity factor synthesis factor degradation

\[
\frac{dCA(t)}{dt} = k_d \left[ \frac{CA_{\text{norm}}}{1 + \left( \frac{C_s(t)}{C_{50,s}} \right)^\gamma} - CA(t) \right]
\]

- \(k_d\) = clotting factor degradation rate constant
- \(CA_{\text{norm}}\) = normal clotting activity
- \(C_{50,s}\) = drug concentration giving 50% of maximum effect
- \(\gamma\) = slope factor
- \(C_s(t)\) = plasma concentration of s enantiomer
Prospective study

n  5 normal male volunteers

Study design  15mg single dose followed by maintenance dosing from day 3 to day 16 designed to achieve 50% of clotting factor activity

Maintenance dose  \( DM/\tau = k_s \cdot V_s \cdot C_{50,s} \)
Dose prediction

\[ \Phi_i = \sum_{k=1}^{nparm} \frac{(\log \hat{p}_k - \log p_{k,i})^2}{cv(\hat{p}_k)^2} + \sum_{j=1}^{nobs_i} \frac{(\log y_{j,i} - \log f_{j,i})^2}{cv(y_{j,i})^2} \]

pharmacokinetic parameters set to population values
Approaches for population analysis

• Naïve pooled data approach
• 2-stage approach
• A fully population approach
Naïve Pooled Data Approach

- Estimate parameters for the model assuming all data arise from a single individual
- Can be biased
  - If individuals have different amounts of data
  - If model very nonlinear
- No estimation of variability components
- Influential factors on PK cannot be ascertained
Naive pooled approach

Concentration Axis

Time Axis

Estimate: CL & V

Fit to all data
Two-Stage Approach

- The “traditional” approach for PK analyses
- Model the PK of each subject’s data (Stage 1)
- Obtain summary statistics, e.g. mean value of clearance (Stage 2)
  - Between-subject variance is overestimated because estimation of the parameters includes residual error
  - Assumes all individuals contribute equally
  - Is not helpful for identifying sources of variability (e.g. renal function)
  - Essentially unusable where there are “sparse” data
Two-Stage Approach

Estimate: $CL \ & \ V$ for each individual
The population approach

- Estimate the overall mean parameters and the variability between individuals as well as the residual variability
- The “standard” population analytical approach
- Sparse/rich, unbalanced/unstructured data
- Considers the population (rather than the individual) as the unit for the PK analysis
- “Individuality” of the subjects is maintained
The population approach

Prediction at population mean parameter estimates for CL & V
The population approach

![Graph showing concentration over time with predictions at population mean and individual estimates for CL & V, and the difference between population mean and individual estimate.](image-url)
The population approach

- Prediction at population mean parameter estimates for $CL$ & $V$
- Difference between population mean and individual estimate
- Difference between individual predicted and individual observed
Variability

• Two levels
  – Variability between people (heterogeneity)
  – Uncertainty about the observations (residual unexplained variability)
Heterogeneity
(Between Subject Variance [BSV])

• There are two sources of heterogeneity between patients
  – Predictable = BSVP
  – Unpredictable (random) = BSVR

• Predictable variability can arise from (examples):
  – differences in renal function
  – differences in body size and composition

• The population parameter variability (PPV) in the population is therefore the sum of these two sources:

\[ \text{PPV} = \text{BSVR} + \text{BSVP} \]
Residual unexplained variability
[RUU]

• This is the variability of the observed concentration around the model predicted
• The observed will seldom equal the model predicted due to many process such as assay error
Nonlinear mixed effects modelling

• Nonlinear: almost (if not all) PK and PKPD models are nonlinear in the parameters
• The population approach is interested in the mean parameter values (“fixed effects”) as well as the variability between and within individuals (“random effects”)
• Combining fixed and random effects is termed “mixed effects”
• Essentially all population PK studies are therefore examples of nonlinear mixed effects modelling
Software for Population Analyses

Decreasing Market Share

- NONMEM ($$)
- Monolix (free/$$)
- WinBUGS (free)
- SAS proc nlmixed ($$$)
- Phoenix nlme (free/$$$)
- S-ADAPT MC-PEM (free)
- NPEM (free)
- P-Pharm ($?)
- NPML (dead?)

Not used to any extent
Role of Modelling and Simulation in Phase I Drug Development

L. Aarons, M. Karlsson, F. Mentré, F. Rombout, J.-L. Steimer, A. van Peer

COST B15
Brussels January 10-11, 2000
When is the population approach useful?

Essentially it is (almost) always useful

- In particular if there are few observations per patient e.g.
  - Outpatients or phase III studies
  - Intensive and emergency care
  - Elderly
  - Children, including premature infants

- When you want to learn about sources of variability
- When you want to develop a model to predict future patient responses
- When you want to use the model to simulate various dosing scenarios
- ...
Tolerability studies
Unbalance and confounding

![Graph showing concentration over time for different subjects with LOQ indicated.](image-url)
Non-linear PK
Rich + sparse data

![Graph showing concentration over time]

- **Concentration**
  - **Total concentration**
  - **Free concentration**
Summary

• PK/PD is model driven
• PK/PD models aid the interpretation of pharmacological data and can be used prospectively to design subsequent studies learning/confirming
• Nonlinear mixed effects modelling allows data from a variety of unbalanced, sparse designs to be analysed
• Software for nonlinear mixed effects modelling is now widely available - even for amateurs!