POPULATION PHARMACOKINETICS

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Population Pharmacokinetics

Definition

Advantages/Disadvantages

Objectives of Population Analyses

Impact in Drug Development

Definition

Population pharmacokinetics describe

-The typical relationships between physiology (both normal and disease altered) and pharmacokinetics/pharmacodynamics,
-The interindividual variability in these relationships, and
-Their residual intraindividual variability.

Sheiner-LB
Drug-Metab-Rev. 1984; 15(1-2): 153-71

Definition

E.g.: A simple Pk model

Equation for plasma concentration (Cp)

Ri = infusion rate
Cl = drug clearance
k =elimination rate constant
ε = measurement error, intra-individual error

Chart showing drug conc over time

Definition

Equations

Chart showing drug conc versus time curves with continuous infusion.

Steady-state equations for Cp and CL.

Definition

Cl = metabolic clearance + renal clearance

$Cl = \Theta_1 + \Theta_2 \bullet CCr \pm \eta$

Graph showing drug conc over time and drug clearance correlation with creatinine clearance

Definition

Cl = metabolic clearance + renal clearance

$$Cl = \Theta_1 + \Theta_2 \bullet CCr \pm \eta$$

Equation

Chart showing drug clearance correlation with creatinine clearance

Graphical illustration of the statistical model used in NONMEM for the special case of a one compartment model with first order absorption. (Vozeh et al. Eur J Clin Pharmacol 1982;23:445-451)

Graph

Objectives

1. Provide Estimates of Population PK Parameters (CL, V) - Fixed Effects

2. Provide Estimates of Variability - Random Effects

   -Intersubject Variability
   -Interoccasion Variability (Day to Day Variability)
   -Residual Variability (Intrasubject Variability, Measurement Error, Model Misspecification)

Objectives

3. Identify Factors that are Important Determinants of Intersubject Variability

-*Demographic:* Age, Body Weight or Surface Area, gender, race
-*Genetic:* CYP2D6, CYP2C19
-*Environmental:* Smoking, Diet
-*Physiological/Pathophysiological:* Renal (Creatinine Clearance) or Hepatic impairment, Disease State
-*Concomitant Drugs*
-*Other Factors:* Meals, Circadian Variation, Formulations

Advantages

Sparse Sampling Strategy (2-3 concentrations/subject)

- Routine Sampling in Phase II/III Studies
- Special Populations (Pediatrics, Elderly)

Large Number of Patients

- Fewer restrictions on inclusion/exclusion criteria

Unbalanced Design

- Different number of samples/subject

Target Patient Population

- Representative of the Population to be Treated

Disadvantages

Quality Control of Data

- Dose and Sample Times/Sample Handling/ Inexperienced Clinical Staff

Timing of Analytical Results/Data Analyses

Complex Methodology

- Optimal Study Design (Simulations)
- Data Analysis

Resource Allocation

Unclear Cost/Benefit Ratio

Models are critical in sparse sampling situations:

Chart showing drug conc over time

Models are critical in sparse sampling situations:

Chart showing drug conc over time – Two populations?

Models are critical in sparse sampling situations:

Chart showing drug conc over time (single curve fit for all data).

Models are critical in sparse sampling situations:

Chart showing drug conc over time (2 curves fit 2 sets of the data points)

Models are critical in sparse sampling situations:

Chart showing drug conc over time (3 curves fit 3 sets of data points).

Models are critical in sparse sampling situations:

Chart showing drug conc over time (4 curves fit 4 sets of data points).

Study Objectives

- To evaluate the efficacy of drug treatment or placebo as add on treatment in patients with partial seizures.

Data Structure

Chart with range of doses for 3 studies.

Boxplot of seizure rate versus dose

Illustration showing seizures per month by baseline, placebo, and a dose of 50, 150, 300, and 600 mg.

Count Model

Equation

λ represents the expected number of events per unit time

$$E(Y_{ij})=\lambda_{i}t_{ij}$$

The natural estimator of λ is the overall observed rate for the group.

Formula

Suppose there are typically 5 occurrences per month in a group of patients:- $\lambda=5$

Equation

Graph

Equation

The mean number of seizure episodes per month (λ) was modeled using NONMEM as a function of drug dose, placebo, baseline and subject specific random effects.

Formula

Baseline = estimated number of seizures reported during baseline period
Placebo = function describing placebo response
Drug = function describing the drug effect
η = random effect

Initial Model

Formula

Formula

BASE= 10.8 (9.9,11.7)
ED50 = 48.7 (0,129.1)
Emax = 0.38 (0.15,0.61)
PLAC= -0.1(-0.22,0.02)
ω1 = 1.1 (1.0,1.18)

Sub-population analysis

-Some patients are refractory to any particular drug at any dose.

-Interest is in dose-response in patients that respond

-Useful in adjusting dose in patients who would benefit from treatment

-Investigate the possibility of at least two sub-populations.

Mixture Model

A model that implicitly assumes that some fraction p of the population has one set of typical values of response, and that the remaining fraction 1-p has another set of typical values

Population A (p)

$\lambda_1 = \text{Baseline}_1 + \text{placebo}_1 + \text{drug}_1 + \eta_1$

Population B (1-p)

$\lambda_2 = \text{Baseline}_2 + \text{placebo}_2 + \text{drug}_2 + \eta_2$

Final Model

Population A = 75%

Formula

Population B = 25%

Formula

Patients demonstrating dose-response (75%)

Chart showing monthly seizure frequency (median and quartiles) by dose of baseline, placebo, 50 mg, 150 mg, 300 mg, and 600 mg.

Observed and predicted values.

Patients not demonstrating dose-response (25%)

Chart showing monthly seizure frequency (median and quartiles) by dose of baseline, placebo, 50 mg, 150 mg, 300 mg, and 600 mg.

Observed and predicted values.

Expected percent reduction in seizure frequency

- Monte Carlo simulation using parameters and variance for Subgroup A

- 8852 individuals (51% female)

- % reduction from baseline seizure frequency calculated

- Percentiles calculated for % reduction in seizure frequency at each dose

Percent Reduction in Seizure Frequency

Responding Patients

Graph showing % Reduction in Seizure Frequency over pregabalin doses ranging from 0 to 700 mg.

Results

Estimated population parameters for the exposure-response relationship of seizure frequency to pregabalin or gabapentin dose

Chart with parameter values.

Conclusions

- A comparison of the dose-response relationship for gabapentin and pregabalin reveals that pregabalin was 2.5 times more potent, as measured by the dose that reduced seizure frequency by 50% (ED50).

- Pregabalin was more effective than gabapentin based on the magnitude of the reduction in seizure frequency (Emax)

- Three hundred clinical trials for each drug were simulated conditioned on the original study designs. Each simulated trial was analyzed to estimate % median change in seizure frequency. The observed and model-predicted treatment effects of median reduction in seizure frequency for gabapentin and pregabalin are illustrated for all subjects and for responders. Data points represent median percentage change from baseline in seizure frequency for each treatment group (including placebo). The shaded area corresponds to predicted 10th and 90th percentiles for median change from baseline in seizure frequency.

Relationship Between % Change in Seizure Frequency (Relative to Baseline) and Daily Dosage of Gabapentin and Pregabalin

Chart showing median % Change in Seizure Frequency from Baseline over dose ranging from 0 to 1800 mg/Day

Relationship Between % Change in Seizure Frequency (Relative to Baseline) and Daily Dosage of Gabapentin and Pregabalin in Responders to Treatment

Chart showing median % Change in Seizure Frequency from Baseline over dose ranging from 0 to 1800 mg/Day

Clinical Trial Simulation

- Used to assess how different design and drug factors may affect trial performance.
- May be viewed as an extension of statistical design evaluation.

Planning Phase 2 POC for Alzheimer's Disease Drug

Because the mechanism of action of CI-1017 was untested clinically, the principle objective of the clinical study was to ascertain whether CI-1017 improved cognitive performance at least as fast and as well as tacrine.
This would be considered proof of concept (POC).

Typical Effectiveness Trials (AD)

- Parallel group design
- Two to four treatment groups + placebo
- Powered to detect 3 point improvement in ADAS-Cog
- Minimum 12 weeks of treatment

- Require about 80 subjects per dose group to have 90% power (2 sided 50% sig. Level)

Simulation Model

ADAS – Cog = BASELINE + DISEASE PROGRESSION + PLACEBO + DRUG + ε

Drug effect models considered in simulations study. Parameters characterizing the model are displayed in the individual panels (Lockwood et al.)

4 charts illustrating this.

TRIAL DESIGN

Chart

DATA EVALUATION

DOES THE DRUG WORK?

- AOV to test null hypothesis of no drug effect
- Rejection of null hypothesis judged correct
- Dose trend test

IS THE SHAPE MONOTONIC OR U-SHAPED?

- Similar to the above two steps
- Non-positive trial pattern classified as flat
- Inference between monotonic and u-shaped based on highest dose having best mean outcome.

SIMULATION

- 100 Trial simulations
- Pharsight trial simulator (TS2)
- Data from each trial analyzed
- Conclusions scored

DRUG EFFECT

Percent of 100 trials (power) that detected a drug effort for design number 6, 7 and 8.

Chart

SHAPE

Percent of 100 trials (power) that correctly identified dose-response shape for design number 6, 7 and 8

Chart

Simulation Conclusions
Design

4x4 LS with 4-week periods using bi-weekly measurements

- Was best among alternatives considered for detecting activity and identifying DR shape
- Met minimum design criteria (80% average power)

Results

4x4 LS design was accepted, conducted, and analyzed more-or-less as recommended

Unfortunately, drug didn’t work

- But we were able to find this out more quickly and with less resources than with conventional design

Gabapentin – Neuropathic Pain
NDA

- Two adequate and well controlled clinical trials submitted.

- Indication – post-herpetic neuralgia

- Trials used different dose levels
    - 1800 mg/day and 2400 mg/day
    - 3600 mg/day

- The clinical trial data was not replicated for each of the dose levels sought in the drug application

FDAMA 1997

FDA review staff decided to explore whether PK/PD analyses could provide the confirmatory evidence of efficacy.

"—based on relevant science, that data from one adequate and well controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness."

Gabapentin Study Designs for PHN

Overview of PHN Controlled Studies: Double-Blind Randomized/Target Dose and ITT Population

Chart

- Used all daily pain scores (27,678 observations)
- Exposure-response analysis included titration data for within-subject dose response

Gabapentin Response in PHN

Two graphs showing mean pain score over time (Days)

Time Dependent Placebo Response, Emax Drug Response and Saturable Absorption,

Results

- Summary statistics showed pain relief for both studies at different doses concur.

- M & S showed pain scores for both studies can be predicted with confidence from the comparative pivotal study (cross confirming).

Conclusion

- The use of PK/PD modeling and simulation confirmed efficacy across the three studied doses, obviating the need for additional clinical trials.

- Gabapentin was subsequently approved by FDA for post-herpetic neuralgia

- The package insert states “pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses”

Issue

A new α2δ ligand (PD0332334) that has anxiolytic properties was in development.

Little was known about AE's for this compound, however, extensive knowledge from other α2δ ligands (pregabalin) available.

It is generally believed that dose titration may reduce AE's.

Questions

Would AE frequency be different if the drug was titrated to the target dose?

How long do we need to titrate to minimize AE's?

How many dose steps do we need to minimize AE's?

Objectives

To describe the exposure-longitudinal AE severity relationship following multiple doses of pregabalin.

To describe the relationship between AE and patient dropout

To explore the relationship between dose titration of pregabalin and dropout

Frequency of dizziness by day and dose

Nine graphs illustrating this.

Observed and Predicted
Conditional Severity Model with Markov

7 Graphs illustrating this

Simulation Step
(example: Time-course of incidence)

Illustration of the probability of incidence, “Mean of trial” and “Summary of Mean”.

Simulation (≥mild)
Severity Model with Markov

8 graphs illustrating that Simulated Probabilities Are Presented By Means with 95% CI and 80 %CI from 100 Simulations.

Simulation (≥ moderate)
Severity Model with Markov

7 graphs illustrating Simulated Probabilities Are Presented By Means with 95% CI and 80 %CI from 100 Simulations.

Simulation (≥severe)
Severity Model with Markov

7 graphs illustrating that Simulated Probabilities Are Presented By Means with 95% CI and 80 %CI from 100 Simulations.

>=mild

5 graphs illustrating the maximum (peak) mean probability for each scenario with 1-6 weeks titration periods.

>=moderate

5 scenarios illustrating the maximum (peak) mean probability for each scenario with 1-6 weeks titration periods.

>=severe

5 scenarios showing the maximum (peak) mean probability for each scenario with 1-6 weeks titration periods.

Simulated GAD survival probabilities from the combined Dizziness-dropout model. Two dosing schemes (blue) within a weeklong titration regimen differ only over 3 initial days of dosing.

Two charts illustrating this.

Summary

Population PK/PD quantifies and allows prediction of the variability in drug response in the population of interest.

It enables optimizing the dosage regimen in the target population.

Population PK/PD is an essential tool to improve the efficiency and to facilitate decision making in drug development and regulatory assessment.