Crossover trials with two periods and two sequences

Standard approach (FDA[1] and EMEA[2])

Compute AUC and Cmax by non compartmental analysis

Test on log parameters
  • Using linear mixed effects model with treatment, period, sequence, and subject effects
  • Needs >10 samples per subject

Nonlinear mixed effects models (NLMEM)[3,4]

Simultaneous data analysis for all subjects

Few samples per subject → study on patients

Objectives: mimic the standard bioequivalence analysis using NLMEM and Wald test

Methods

NLMEM bioequivalence analysis mimicking NCA analysis

Statistical model
  • Parametric pharmacokinetic (PK) model
  • Between (BSV) and within subject variability (WSV) on all PK parameters
  • Treatment (β), period, and sequence effects on all PK parameters

Parameter estimation by maximum likelihood
  • SAEM algorithm implemented in MONOLIX 2.4[5,6]

Bioequivalence Wald test
  • Schuirmann’s test[7]: H0: [β ≤ log(0.8) or β ≥ log(1.25)]
  • Rejection of H0: CL/βCmax/log(0.8) > log(0.8), log(1.25)
  • CI/βCmax computed from the estimated treatment effect and its standard error (SE)

Wald test on secondary parameters[8]
  • βAUC = −βCL, linear PK (→ SE(βCL) = SE(βCmax))
  • βCmax: nonlinear function of fixed effects (→ estimation of SE(βcmax)) by delta method[9] or by simulation using the parameter estimates and the Fisher information matrix estimate

Simulation study
  • One-compartment model (parameters k, CL/F, V/F)
  • Crossover trials with two periods and two sequences

Designs
  • Rich: N=40, n=10
  • Original: N=12, n=10
  • Intermediate: N=24, n=5
  • Sparse: N=40, n=3

Treatment effect on CL/F and V/F
  • 1000 simulations under H0: βAUC/log(0.8) and βCL/log(0.8)
  • 1000 simulations under H0: βAUC/log(1.25) and βCL/log(1.25)

Two levels of variability
  • For the random effects
    | BSV | WSV |
    |-----|-----|
    | S0  | 10%  |
    | S0  | 20%  |
    | S0  | 50%  |

For the error model
  • σ (mg/l)  b
  | S1 | 0.1 | 10% |
  | S1 | 1   | 23% |

S1 and S2 simulations with the 4 designs

S3/4 simulations with the intermediate design

Concentrations (ng/ml) simulated with the four designs under S3 for the reference treatment

Evaluation of the estimates

AUC and Cmax

Bioequivalence Wald test performed with the estimated and empirical SE

Evaluation of the treatment effect on AUC and Cmax obtained from NCA

AUC and Cmax compared to the simulated value

βAUC, βCmax, SE(βAUC) and SE(βCmax)

Boxplot of the effect estimates of AUC and Cmax obtained from NCA

Conclusion

Bioequivalence analysis by NCA
  • Bias in the geometric means of AUC and Cmax for sparse design
  • Good properties of the test except for high variability

Bioequivalence analysis by NLMEM
  • Good estimation of the population estimates even for sparse design
  • Good properties of the test for rich design (asymptotic conditions)
  • Correction of the test for small sample size needed (linked to the underestimation of the SE)
  • Applicable to nonlinear pharmacokinetics (biologic drugs) and to sparse design