*S-4 [15:20~15:50]*

# 생물학적 동등성시험에서 사용되는 통계방법에 대한 고찰

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* Bioavailability of a drug:

the rate and extent to which the active ingredient is absorbed and becomes available at the site of drug action

* brand-name drug vs generic drug
* ANDA

* AUC (Area Under the Curve)

$C_0, C_1, , , , C_k$ : plasma concentration obtained at time $0, t_1, , , , , t_k$

$$AUC(0-t_k) = \sum_{i=2}^{k} \frac{C_{i-1}+C_i}{2}(t_i - t_{i-1})$$

$$AUC(0-\infty) = AUC(0-t_k) + C_k/k_e$$

$k_e$ : elimination rate

Assumption:

When two drugs products are equivalent in the rate and extent to site of drug action, it is assumed that they will be therapeutically equivalent.

* The comparison of the first moment (mean) of the distribution of the pharmacokinetic parameters (say, AUC$(0-\infty)$) for the two drug products refers to the comparison of "average bioavailability".

* Parallel Design vs Crossover Design

* intersubject variability

  intrasubject variability

* Crossover design removes the intersubject variability and use only intra-subject variablility.

* 2 x 2 Crossover Design

  We wish to compare formulation A and B.

  We make two sequences.

  sequence 1 : A → B

  sequence 2 : B → A

  We assign $n_1 + n_2$ subjects randomly.

  $n_1$ subjects are assigned to sequence 1

  $n_2$ subjects are assigned to sequence 2

| | period1 | washout | period2 |
|---|---|---|---|
| sequence 1 | A | . | B |
| sequence 2 | B | . | A |

* carryover effect

* Statistical Model

$$Y_{ijk} = \mu + S_{ik} + P_j + F_{j,k} + C_{(j-1,k)} + e_{ijk}$$

where

$\mu$ : overall mean

$S_{ik}$ : random effect of the ith subject in the kth sequence

$P_j$ : fixed effect of jth period

$F_{j,k}$: drug effect

$C_{(j-1,k)}$: carryover effect

$e_{ijk}$ : random error

$S_{ik} \sim N(0, \sigma_s^2)$

$e_{ijk} \sim N(0, \sigma_e^2)$

$S_{ik}$ and $e_{ijk}$ are independent.

* 2 x 2 Crossover Design

| sequence | period I | period II |
|---|---|---|
| 1 (RT) | $\mu+P_1+F_R$ | $\mu+P_2+F_T+C_R$ |
| 2 (TR) | $\mu+P_1+F_T$ | $\mu+P_2+F_R+C_T$ |

* Test for Carryover Effects

Consider sum of observations in two periods.

$$U_{ik}=Y_{i1k}+Y_{i2k} \quad : \quad i=1,,,n_k, \quad k=1,2$$

$$U_{i1} \sim N(2\mu+C_R, \sigma_u^2), \quad i=1,,,n_1$$

$$U_{i2} \sim N(2\mu+C_T, \sigma_u^2), \quad i=1,,,n_1$$

where

$$\sigma_u^2=2(2\sigma_s^2+\sigma_e^2)$$

Let $\overline{U_{.k}}=n_k^{-1}\sum_{i=1}^{n_k}U_{ik}, \quad k=1,2$

$$\widehat{\sigma_u^2}=\sum_{k=1}^{2}\sum_{i=1}^{n_k}(U_{ik}-\overline{U_{.k}})^2$$

$$T_c=\frac{\overline{U_{.2}}-\overline{U_{.1}}}{\widehat{\sigma_u}\sqrt{n_1^{-1}+n_2^{-1}}}$$

Carryover effect exists if

$$|T_c| > t(\alpha/2, n_1+n_2-2)$$

* Test for Average Bioequivalence

Responses such as AUC are usually positively skewed.

→ Not normal distribution

Take Log transformation!!!

Let $Y^{*}_{ijk} = \ln(Y_{ijk})$

$$\overline{Y^{*}_{R}} = 2^{-1}(\overline{Y_{.11}} + \overline{Y_{.22}})$$

$$\overline{Y^{*}_{T}} = 2^{-1}(\overline{Y_{.12}} + \overline{Y_{.21}})$$

The 90% confidence interval is $(L_1, U_1)$, where

$$L_1 = (\overline{Y^{*}_{T}} - \overline{Y^{*}_{R}}) - t(\alpha, n_1 + n_2 - 2)\,\hat{\sigma}_d \sqrt{n_1^{-1} + n_2^{-1}}$$

$$U_1 = (\overline{Y^{*}_{T}} - \overline{Y^{*}_{R}}) + t(\alpha, n_1 + n_2 - 2)\,\hat{\sigma}_d \sqrt{n_1^{-1} + n_2^{-1}}$$

We conclude that two formulations are average bioequivalent if

$L_1 > \ln(0.8) = -0.2231$ and

$U_1 < \ln(1.25) = 0.2231$

* Westlake's symmetric confidence interval
* Confidence interval based on Fieller's theorem
* Chow and Shao's confidence interval

## — Interval Hypotheses Testing —

* Usual hypothesis testing

$H_0: \mu_T = \mu_R$ *vs* $H_1: \mu_T \neq \mu_R$

* In Bioequivalence

$H_0: \mu_T \neq \mu_R$ *vs* $H_1: \mu_T = \mu_R$

$H_0: \mu_T - \mu_R \leq \theta_L$ or $\mu_T - \mu_R \geq \theta_U$

vs $H_1: \theta_L < \mu_T - \mu_R < \theta_U$

where $\theta_L$ and $\theta_U$ are some clinically meaningful limits.

* The above hypotheses are decomposed into two sets of one-sided hypotheses.

$H_{01}: \mu_T - \mu_R \leq \theta_L$ vs $H_{11}: \mu_T - \mu_R > \theta_L$

and

$H_{02}: \mu_T - \mu_R \geq \theta_U$ vs $H_{12}: \mu_T - \mu_R < \theta_U$

If we reject $H_{01}$ and $H_{02}$, then we conclude $\theta_L < \mu_T - \mu_R < \theta_U$

* Schuirman's Two One-Sided Procedure

We conclude that two formulations are bioequivalent if

$$\frac{(\overline{Y^*_T} - \overline{Y^*_R}) - \theta_L}{\hat{\sigma}_d \sqrt{n_1^{-1} + n_2^{-1}}} > t(\alpha, n_1 + n_2 - 2)$$

and

$$\frac{(\overline{Y^*_T} - \overline{Y^*_R}) - \theta_U}{\hat{\sigma}_d \sqrt{n_1^{-1} + n_2^{-1}}} < -t(\alpha, n_1 + n_2 - 2)$$

* Nonparametric Methods

When assumption of normality (for raw data or for log-transformed data) is violated, let

$d_{ik} = 2^{-1}(Y_{i2k} - Y_{i1k})$,

$i = 1, , , , n_k$, $k = 1, 2$

"period difference"

Let

$b_{hik} = d_{ik} - \theta_h$, $h = L, U$

for subjects in sequence 1

$b_{hik} = d_{ik}$

for subjects in sequence 2

For a fixed $h = L, U$, $b_{hi1}$ and $b_{hi2}$ have the same distribution except for the mean difference.

We can construct Wilcoxon rank sum test based on the ranks of $b_{hi1}$ and $b_{hi2}$.

$R(b_{Lik})$ = rank of $b_{Lik}$ in the combined sample $b_{Lik}$, $i = 1, , , n_k$, $k = 1, 2$

$W_L = R_L - 2^{-1} n_1 (n_1 + 1)$

We reject $H_{01}$ if $W_L > w(1-\alpha)$

* Power of Schuirman's two one-sided t test procedure

* The conclusion of bioequivalence based on only average bioavailability may be misleading.

We need to investigate the assessment of equivalence in variabilities of bioavailability between two formulations.