Integration of non-compartmental analysis and biological equivalence test using EDISON Science Apps

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Abstract

The bioequivalence test is performed when existing drugs patents are expired and companies develop drugs to sell on the same conditions as existing drugs. The existing original drug (reference) and newly developed drug (test) are administered in the form of a crossover study, and the pharmacokinetic parameters obtained from the blood concentration are compared and evaluated. Statistics are playing a key role in assessing bioequivalence, and statistical analysis requires computer software. But each software is difficult to use, complex, and expensive. It is especially difficult to use for beginners of pharmacokinetic analysis or non-statisticians. So we integrate this process as a continuous process using the EDISON Science App. It is intended to show that the method presented in this study enables fast, accurate, and cost-effective rapid non-compartmental analysis and biological equivalence analysis. The aim of this study is to show that it is possible to perform simple, accurate and cost-free rapid non-compartmental analysis and biological equivalence analysis through this proposed method using EDISON Science App. The EDISON Science Apps used in the analysis are two types (NonCompartEdison and edisonBE). Each component is released as an R package named 'NonCompart' and 'BE'. In general, the 2x2 cross-over design is the most basic design (usually RT / TR) in the bioequivalence model. Subjects were randomly divided into two groups. Each group was given the same control and test drug (first dose), and blood samples were collected at each time interval before and after each dose. Data were constructed using the pharmacokinetic parameters obtained from the simulation, and the columns of data are SUBJ (subject ID), GRP (Group), PRD (Period), TRT (Planned time), TIME (Actual time), and CONC (Concentration). In order to perform the bioequivalence analysis as above, the data of SEQ (sequence), TRT (treatment), SUBJ (subject), and PRD (period) must be presented in column form, which is a kind of pharmacokinetic parameter data used in the edisonBE app. Non-compartmental analysis was carried out through the NonComaprt application, and the obtained pharmacokinetic parameters were processed through the edisonBE application. The results are exactly the same as the SAS software results that are used as the standard for evaluating biological equivalence This study presents an easy, accurate, and cost-effective methodology for rapid non-compartmental analysis and bioequivalence analysis using EDISON Science Apps. Nowadays, for this analysis, you have to go through complex steps that require several commercial software. Therefore, the analysis time is long and the cost is high. The authors used EDISON Science Apps to integrate these two processes, enabling continuous analysis from concentration-time data to non-compartmental analysis and bioequivalence analysis.

Keywords: Bioequivalence test, Non-compartment analysis, EDISON science app

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Introduction

The bioequivalence test is a clinical trial conducted when an existing medicine patent expires and the company wants to develop same kind of drug for sale. [1] After the existing original drug (Reference) and newly developed drug (Test) are administered in the form of a crossover study, the pharmacokinetic parameters obtained from the blood concentrations were compared and evaluated.

If the sample is blood, the comparative evaluation items are AUC_t, C_{max} for single does, AUC_t, $C_{ss,\ max}$ for repeated administration. T_{max} was added as a comparative evaluation parameter for agents showing fast drug action such as nitroglycerin sublingual tablet.

When the geometric mean ratio of the calculated curve area (AUC) and peak concentration (Cmax) between the reference drug and test drug is within 0.8 to 1.25, two medicines are evaluated as equal [2]

Statistics are playing a key role in conducting bioequivalence test, however, each software[3] is difficult to use, complicated and expensive especially for beginner or non-statistical students. We integrate this process into a continuous processes using the EDISON Science Apps.

It is intended to show that the method presented in this study enables fast, accurate, and cost-effective rapid non-compartmental analysis and biological equivalence analysis.

Method and Calculation

EDISON science app and R package

EDISON Science Apps to be used in this analysis are of two types: NonCompartEdison and edisonBE. Each app conducts non-compartmental analysis and statistical analysis of bioequivalence, and these apps are programmed as R-based. Each is released as an R package named NonCompart and BE. Each app is released as an R package named NonCompart and BE.

Structure

$Yijk = \mu + Sik + Pj + Fj,k + C(j - 1, k) + \varepsilon ijk$

μ; Overall average, Sik; the effect of the ith subject in the kth sequence (random),

Pj; Effect of the jth period (fixed), Fj, k; he effect of the formulation of the jth period in the kth sequence (fixed), C(j-1,k); C Residual effect of the (j-1) th period in the kth sequence (fixed), εijk : the error term.

Assumption

Sik ~ $N(0,\sigma s^2)$, 2) εijk ~ $N(0,\sigma e^2)$, 3) Sik and εijk가 are independent.

It can be concluded that when the $(1-2\alpha) \times 100\%$ confidence interval for (μT - μR) falls within ln (0.8), ln (1.25), the two agents are biologically equivalent

SAS code

SAS provides the largest and most diverse analysis among statistical packages and is used as a standard for determining bioequivalence globally. SAS code (PROC GLM, PROC MIXED, SAS version 9.4) for analyzing 2x2 cross design data was created and compared with the results calculated by EDISON Science App.

```
PROC GLM DATA=BE OUTSTAT=STATRES; /* GLM use only
 complete subjects. */
 CLASS SEQ PRD TRT SUBJ;
 MODEL LNAUCL = SEQ SUBJ(SEQ) PRD TRT;
 RANDOM SUBJ(SEQ)/TEST;
 LSMEANS TRT /PDIFF=CONTROL('R') CL ALPHA=0.1 COV
 OUT=LSOUT;
 PROC MIXED DATA=BE; /* MIXED uses all data. */
 CLASS SEQ TRT SUBJ PRD;
 MODEL LNAUCL = SEQ PRD TRT;
 RANDOM SUBJ(SEQ);
 ESTIMATE 'T VS R' TRT -1 1 /CL ALPHA=0.1;
 ODS OUTPUT ESTIMATES=ESTIM COVPARMS=COVPAR;
```

Types and components of data

We tested these apps with one of the most basic designs, the 2x2 cross-over design (usually RT / TR). Subjects are randomly divided into two groups. Each group is given the same reference and test drug (first dose), and blood samples are collected at each time interval before and after each dose. After a sufficient period of time (usually more than 5 times the half-life period), each group is given a different dose of the reference drug and the test drug (second dose), and the same blood sampling and blood concentration are measured.

In this poster, the data were constructed using the pharmacokinetic parameters obtained from the simulation in the above scenario, and the data were configured as shown in Table 1. The data of SEQ (sequence), TRT (treatment), SUBJ (subject), and PRD (period) must be presented in column form and this is used as a primary key in edisonBE app. The individual concentration-time graph of 33 subjects is shown in Figure 1.

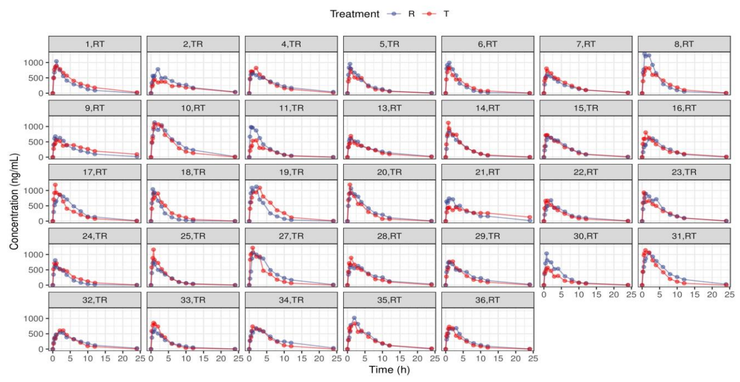

Figure 1. Concentration-time curves of raw data (N=33)

Results

Non-compartmental analysis with NonCompartEdison app

The concentration-time input data (Table 1) is processed through the NonCompartEdison app and the pharmacokinetic parameters are calculated and tabulated. (Table 2). This output data is used as an input for the edisonBE app and is used for biological equivalence analysis.

Table 1. An example of the raw concentration-time data used for EDISON Science Apps. The dataset was simulated based on the 2x2 crossover design

SUBJ	GRP	PRD	TRT	nTIME	TIME	CONC
1	RT	1	R	0	0	0
1	RT	1	R	0.25	0.26	511.3
1	RT	1	R	0.5	0.46	678.79
1	RT	1	R	…	…	…
1	RT	2	T	0	0	0
1	RT	2	T	0.25	0.25	487.62
1	RT	2	T	0.5	0.48	769.6
…	…	…	…	…	…	…
5	TR	1	T	0	0	0
5	TR	1	T	0.25	0.23	382.79
5	TR	1	T	0.5	0.45	477.03
5	TR	1	T	…	…	…
5	TR	2	R	0	0	0
5	TR	2	R	0.25	0.28	596.98
5	TR	2	R	0.5	0.47	832.76
5	TR	2	R	…	…	…
…	…	…	…	…	…	…

Table 2. The raw pharmacokinetic data calculated by NonCompartEdison App

SUBJ	GRP	PRD	TRT	AUClast	Cmax	Tmax
1	RT	1	R	5018.927	1043.13	1.04
1	RT	2	T	6737.507	894.21	1.03
2	TR	1	T	4373.97	447.26	1.01
2	TR	2	R	6164.276	783.92	1.98
4	TR	1	T	5592.993	824.42	1.97
4	TR	2	R	5958.16	646.31	0.97
5	TR	1	T	3902.59	803.7	0.8
5	TR	2	R	4620.156	955.3	0.74

Table 3. Comparison of 90% confidence interval for the ratio of the geometric means of (A) AUC_{last} and (B) C_{max}

(A)

Analysis	Lower Limit	Point Estimate	Upper Limit
EDISON Science App	0.88944	0.95408	1.02341
SAS: PROC GLM	0.88944	0.95408	1.02341
SAS: PROC MIXED	0.88944	0.95408	1.02341

(B)

Analysis	Lower Limit	Point Estimate	Upper Limit
EDISON Science App	0.90136	0.97984	1.06515
SAS: PROC GLM	0.90136	0.97984	1.06515
SAS: PROC MIXED	0.90136	0.97984	1.06515

Evaluating bioequivalence through the edisonBE app

Pharmacokinetic parameters are processed through the edisonBE app and the ANOVA table, variability, Least square mean(LSM), 90% confidence interval of the geomateric mean ratio(GMR), and number of samples are calculated for biological equivalence determination. (Figure 2) The AUC_{last} and C_{max} calculated with this data meets the bioequivalence criteria.

1. ANOVA Table

```
> print(test2x2(NCAResult4BE, "AUClast"), na.print="")
$`Analysis of Variance (log scale)`
                    SS DF          MS           F           p
SUBJECT      2.875497e+00 32 8.985928e-02 3.183942248 0.0008742828
GROUP        1.024607e-01  1 1.024607e-01 1.145416548 0.2927731856
SUBJECT(GROUP) 2.773036e+00 31 8.945279e-02 3.169539016 0.0009544080
PERIOD       3.027399e-05  1 3.027399e-05 0.001072684 0.9740824428
DRUG         3.643467e-02  1 3.643467e-02 1.290972690 0.2645764201
ERROR        8.749021e-01 31 2.822265e-02
TOTAL        3.786834e+00 65
```

2. Variability

```
$`Between and Within Subject Variability`
                          Between Subject Within Subject
Variance Estimate                0.03061507     0.02822265
Coefficient of Variation, CV(%)    17.63193968    16.91883011
```

3. LSM

```
$`Least Square Means (geometric mean)`
                 Reference Drug Test Drug
Geometric Means        5092.098  4858.245
```

4. 90% CI of GMR

```
$`90% Confidence Interval of Geometric Mean Ratio (T/R)`
                Lower Limit Point Estimate Upper Limit
90% CI for Ratio    0.889436       0.9540753    1.023412
```

5. Sample size

```
$`Sample Size`
                      True Ratio=1 True Ratio=Point Estimate
80% Power Sample Size            6                        7
```

Figure 2. Output format of bioequivalence tests performed by BE R package.

Comparison with SAS results for 90% confidence interval

The calculated values obtained by EDISON Science Apps were exactly the same as those of the standard SAS software. (Table 3)

Calculate the number of samples

Analysis with the BE package calculates the Between subject Coefficient of variation(CV) value and the Within Subject CV. Based on these results, we calculated the number of samples with 80% power.

The AUC_{last} CV between the subjects was 17.63% and the within-subject CV was 16.92%. The number of samples with 80% power was 6 for the GMR of 1, and 7 for the point estimate(0.95)(Figure 2)

Conclusion

This study presents an easy, accurate, and cost-effective methodology for rapid non-compartmental analysis and bioequivalence analysis using EDISON Science Apps.

Nowadays, for this analysis, you have to go through complex steps that require several commercial software for this anlysis. (Figure 3) The authors used EDISON Science Apps to integrate these two processes, enabling continuous analysis from concentration-time data to non-compartmental analysis and bioequivalence analysis.

Comparisons with the SAS statistical package, which is that the most accurate assessment of bioequivalence in academia and industry is in this analysis, verified that the bioequivalence analysis using the EDISON Science app provided accurate values.

We expect that EDISON Science Apps are used in pharmacokinetic education which is an essential element of pharmacology and save a lot of money in the clinical trial industry

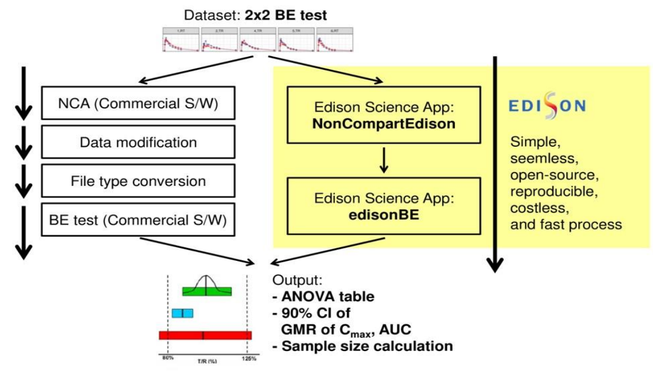

Figure 3. Comparison between a traditional analysis process (left boxes) and the proposed process (right boxes) using EDISON Science Apps.

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