EDISON 사이언스 앱을 사용한 비구획분석과 생물학적동등성 분석의 통합

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전공의 한성필

Introduction: Bioequivalence

- Definition
  - When administered at the **same molar dose** under similar conditions in an appropriately designed study
  - **Absence of a significant difference**
  - At the site of drug action
    - The **rate and extent** to which the **active ingredient or active moiety** in pharmaceutical equivalents or pharmaceutical alternatives

(Source: ICH Guideline)

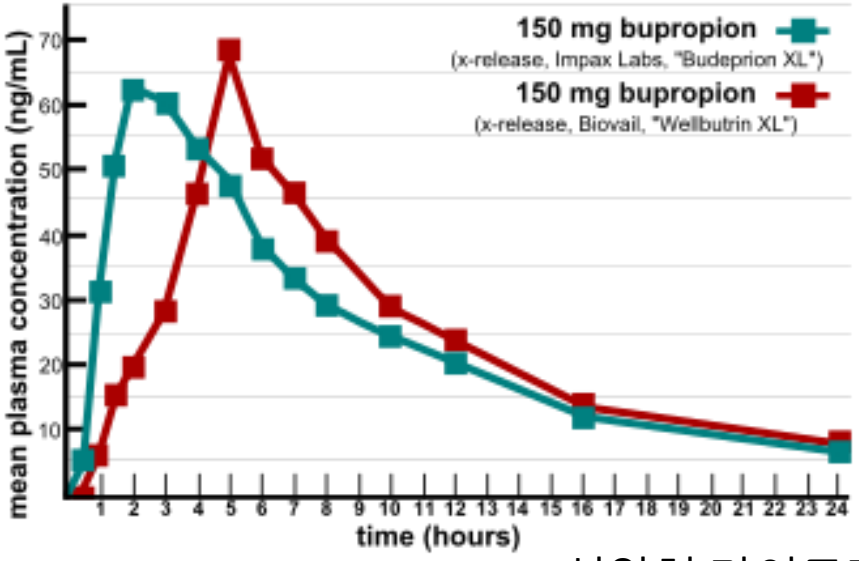
Introduction: Generic Drug

- Drug product which is identical or bioequivalent to Reference drug in:
  - Active ingredient (s)
  - Route of administration
  - Dosage form
  - Strength
  - Indications
  - Safety
- May have different:
  - Inactive ingredients
  - Colour
  - Shape
- Almost half of drugs in market have Generics

(Source: ICH Guideline)

Introduction: Bioequivalence test

- 생물학적동등성시험(bioequivalence test)는 기존 의약품의 특허가 만료된 후, 해당 의약품을 동일하게 개발하여 판매하고자 할 때 수행하는 임상시험.



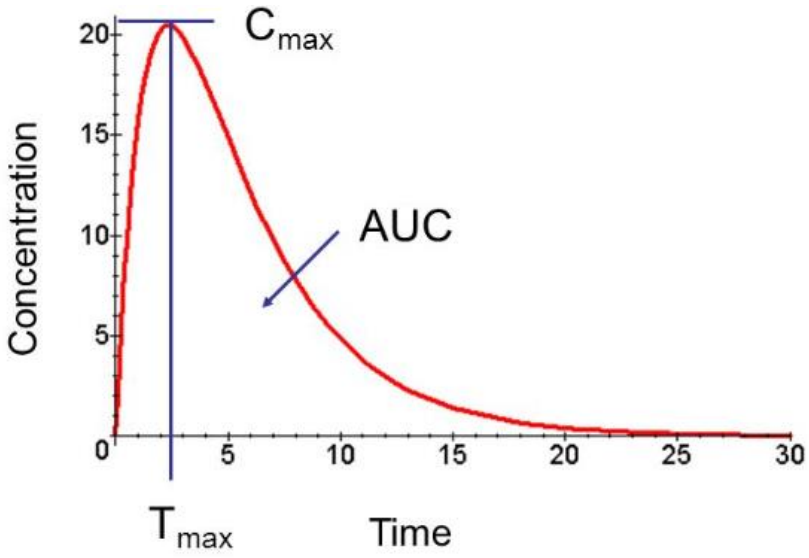
(Source: 식약처 가이드라인)

Introduction: Bioequivalence test

- Study Design
  - Good experimental design, enhances the power of the study
  - Depends on: question to be answered, nature of reference drug/ dosage form, benefit-risk ratio
- As far as possible, the study should be of crossover design & suitably randomized
- Ideal design:
  - Randomized two-period, two-sequence, crossover design with adequate washout period

Introduction: Parameters to be measured

- Pharmacokinetic Parameters measured are:
  - C_{max}
  - $AUC_{0\text{-}t}$
  - $AUC_{0\text{-}\infty}$
  - (T_{max})
- For steady state studies:
  - $AUC_{0\text{-}t}$
  - C_{max}
  - C_{min}
  - Degree of fluctuation



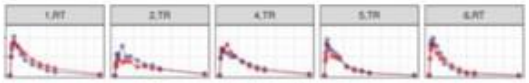
Introduction: Assessment

- PK Parameter
  - log-normal distribution
- Assessment
  - Log-transformed C_{max}
  - Log-transformed $AUC_{0\text{-}t}$
  - geometric mean ratio – 90% confidence Interval
    - 0.80 ~ 1.25

서론

- 각각의 소프트웨어가 사용하기 어렵고 과정이 복잡하며 큰 비용이 소모. 특히 약동학 분석 초보자나 통계학 비전공자가 사용하기 어려움. 본 저자들은 EDISON 사이언스 앱을 사용하여 이 과정을 연속성을 지닌 한 과정으로 통합.
- 본 연구가 제시하는 방법을 통해 쉽고 정확하고 비용이 들지 않는 빠른 비구획분석과 생물학적 동등성 분석이 가능하다는 것을 보이고자 함.

Dataset: **2x2 BE test**



NCA (Commercial S/W)

Data modification

File type conversion

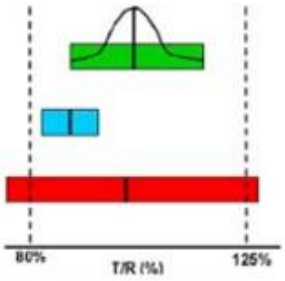
BE test (Commercial S/W)

Edison Science App:
NonCompartEdison

Edison Science App:
edisonBE

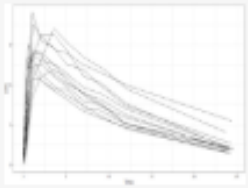
EDISON

Simple,
seemless,
open-source,
reproducible,
costless,
and fast process



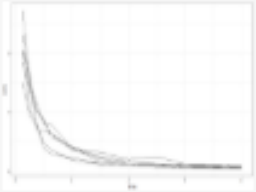
Output:
- **ANOVA table**
- **90% CI of**
  GMR of C_{max}, AUC
- **Sample size calculation**

EDISON Science Apps



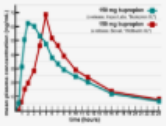
PK 1 Comp Oral

My EDISON 〉pk1coma



PK 1 Comp IV

My EDISON 〉pk1cima

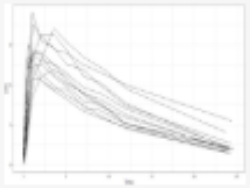


NonCompartEdison: Noncompartmental Analysis for Pharmacokinetic Parameters using...

생물학적동등성 시험 자료 분석 및 시뮬레이션

My EDISON 〉edisonBE

EDISON Science Apps



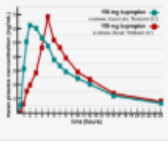
PK 1 Co

My EDISON 〉pk1

nSubj :	10
CL :	30
V :	100
Ka :	2
DH1 :	0, 100000
Time :	0, 0.25, 0.5, 1, 2, 4, 5, 7, 9, 12, 24
PropE :	0.1
AddE :	0.1
LLoQ :	0
Jitter :	1
FullCov :	0.04, 0.03, 0.03, 0.04
concLog :	Linear

PK 1 Comp IV

My EDISON 〉pk1cima



NonCompartEdiso

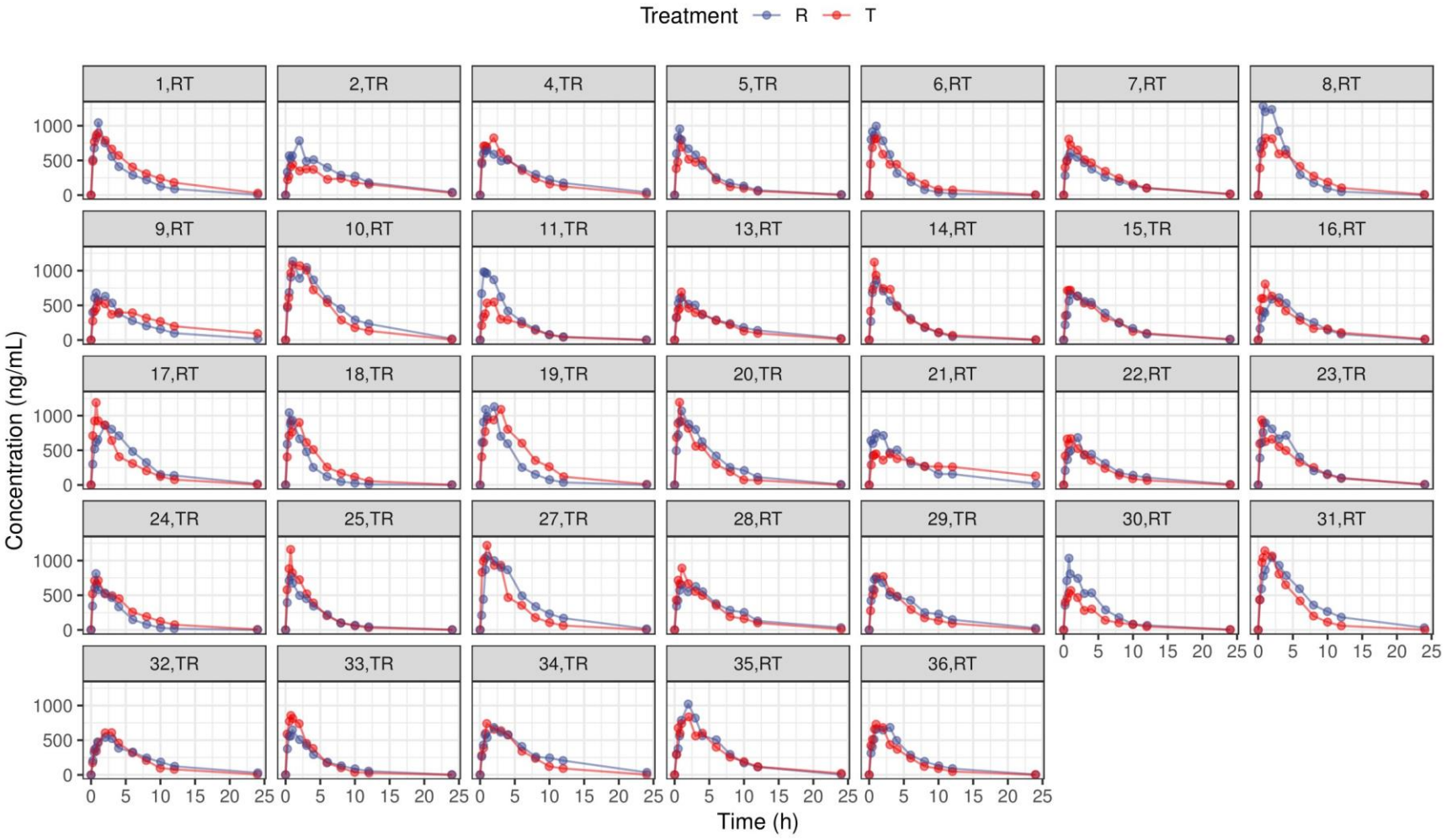
using...

armacokinetic Parameters

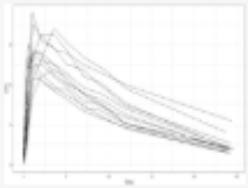
생물학적동등성 시험

My EDISON 〉edisonBE

Simulated Data

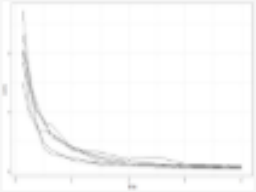


EDISON Science Apps



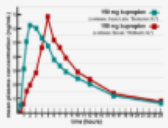
PK 1 Comp Oral

My EDISON 〉pk1coma



PK 1 Comp IV

My EDISON 〉pk1cima



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My EDISON 〉edisonBE

입력 자료의 형태

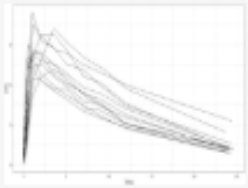
2x2 BE trial	Period 1	Period 2
N=12		
Sequence 1 (BA)	Y_{11}	Y_{12}
BA is RT		
Sequence 2 (AB)	Y_{21}	Y_{22}
AB is TR		

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	…	…	…
…	…	…	…	…	…	…

결과 자료의 형태

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

EDISON Science Apps



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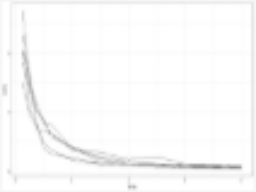

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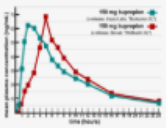

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My EDISON 〉edisonBE

. Comparison of 90% confidence interval for the ratio of the geometric means of (A) AUC_{0-t} 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

결과

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
```

Conclusion

- 본 연구는 EDISON 사이언스 앱을 사용해 쉽고 정확하고 비용이 들지 않는 빠른 비구획분석과 생물학적동등성 분석법을 제시하였다.

- 현재는 이러한 분석을 위해서 여러 상용 소프트웨어를 필요로 하는 복잡한 단계를 거쳐야 한다.
  - 따라서 분석 시간이 오래 걸리고 많은 비용이 소모되었다.
  - 본 저자들은 EDISON 사이언스 앱을 사용하여 이 두 과정을 통합하였고, 이로서 농도-시간 자료로부터 비구획분석과 생물학적동등성 통계분석까지 연속적으로 가능케 하였다.

- 본 분석에서 학계와 산업계에서 가장 정확하게 생물학적 동등성을 평가한다고 말하는 SAS통계 패키지와의 비교를 통해 EDISON 사이언스 앱을 사용한 생물학적 동등성 분석이 정확한 값을 제시함을 검증할 수 있었다.